UNITED STATES DISTRICT COURT

SOUTHERN DISTRICT OF NEW YORK

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TEVA PHARMACEUTICALS USA, INC., TEVA PHARMACEUTICALS INDUSTRIES LTD., TEVA NEUROSCIENCE, INC. and YEDA RESEARCH AND DEVELOPMENT CO. LTD.,

Plaintiffs,

v. 08-CV-7611 (BSJ)

SANDOZ, INC., SANDOZ INTERNATIONAL GMBH, NOVARTIS AG, and MOMENTA PHARMACEUTICALS, INC.,

Defendants.

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TEVA PHARMACEUTICALS USA, INC., TEVA PHARMACEUTICALS INDUSTRIES LTD., TEVA NEUROSCIENCE, INC. and YEDA RESEARCH AND DEVELOPMENT CO. LTD.,

Plaintiffs,

v. 09-CV-8824 (BSJ)

MYLAN PHARMACEUTICALS INC., MYLAN INC., NATCO PHARMA LTD.,

Defendants. Non-Jury Trial

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New York, N.Y.
September 14, 2011
9:40 a.m.

Before:

HON. BARBARA S. JONES,

District Judge

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ALSO PRESENT: CORT CHASE, Litigation Support

(Trial resumed)

MR. SKILTON: Good morning, your Honor.

THE COURT: Good morning, Mr. Skilton, Dr. Zeigler.

MR. ANSTAETT: Your Honor, just one housekeeping matter from yesterday. Your Honor there was a demonstrative exhibit that was admitted for Rule 1006 purposes, and we have a copy of that demonstrative exhibits for the parties. For the record, the exhibit number is DTX 4015.

THE COURT: All right. Mr. Skilton, you may proceed.

ALLEN ZEIGLER,

called as a witness by Defendant, having been previously duly affirmed, testified as follows:

MR. SKILTON: Good morning, Dr. Zeigler.

THE WITNESS: Good morning, Mr. Skilton. Mr. Skilton, there's an object here that's in the middle of the screen. Does it have to be here?

MR. SKILTON: I don't think we can remove it.

THE COURT: I'm not removing Bobby.

THE WITNESS: Whatever this is. I'm sorry. I would never refer to him as a thing. That's much better, thank you.

THE COURT: It's better for you. Now we'll see what it does for everything else.

THE WITNESS: I'm sorry.

THE COURT: No, no.

DIRECT EXAMINATION

BY MR. SKILTON:

Q. Dr. Zeigler, let me to pick up where we left off, establish a couple of things. You described I think generally your Jefferson lab work from the period of December 1969 through the mid-'80s yesterday, so I'll not go back there, but during that period, did you do any work in characterization as you used that term yesterday?

A. Yes. I did some gel chromatography studies of some of my polypeptide products, and I did some molecular weight studies. I didn't do the molecular weight studies by SEC, but by untracentrifugation and by viscosity. I also characterized the materials in terms of secondary structure by circular dichroism.

Q. When you were dealing with your compositions, what were the molecular weight ranges that those compositions were in?

A. Well, with the method of polymerization that I developed, they ranged between an average molecular weight of 5,000, 50,000 approximately.

Q. And yesterday you mentioned that you were working with random copolymers with various constituent elements and that you were synthesizing them. Just briefly describe what you meant by that term.

A. Yes, instead of polymerizing the monomers as the single amino acid, I would synthesize typically tetrapeptide and use the entire tetrapeptide, that is four amino acids, three

peptide bonds, as the monomer to polymerize products of great diversity and different molecular weight sizes.

Q. And you allude to the purpose of your research or goals, so to speak, of that research. Why don't you again if you haven't said it to the detail that I would request, why don't you state the purpose of that research in reference to the kinds of synthetic chemistry that you were working on?

A. Well, these are parameters of a polydispersed system that would be of interest to the readers, obviously, who would want to know a little bit more about such things as the degree of polydiversity, perhaps something about the secondary structures as they relate to secondary structures that are found in proteins.

Q. And you were looking for potential consequences in the immune system, did I understand that correctly?

A. Yes, that was the ultimate goal of the particular group that I was associated with initially at Jefferson.

Q. Now, take that rather general and generic description of your work and compare it to your understanding of the work that the Arnon-Sela group were doing contemporaneously.

A. Their goals were rather similar. Both Drs. Sela and Arnon were top-notch biochemists as well as immunologists. Our interests were quite similar.

Q. By the way, did you know these two scientists?

A. Yes, I did.

Q. And give the Court an example of situations in which you got to know them.
A. Well, Dr. Sela, for example, was a post-doctoral student in Dr. Christian Anfinsen's lab a number of years before I arrived. He would come occasionally to the lab to see what's happening, particularly -- this was, I should say, in my post-doc at MIH, I would see Dr. Sela from time to time and when I joined the faculty at Thomas Jefferson we were invited to international meetings in particular, there's one international meeting in Israel, I believe, it was at a place called Curiata Novim in 1972, again, it may have been 1973 in which the organizers were Drs. Sela, Katchalski and Arnon.
Q. And you mentioned your sabbaticals. Did you see or become acquainted with them in the context of those sabbaticals?
THE COURT: Mr. Skilton, I think I have enough background now, if you want to move forward.
MR. SKILTON: Thank you, your Honor.
Q. What were you asked to do in this case?
A. I was asked to review the copolymer-1 literature, particularly patents '550 as well as '808 and the other patents in suit with regards to the literature, with regards to the claims and offer, render my opinions particularly with regard to obviousness, as I understand it.
Q. Were you asked to make your evaluations and give your opinions from a particular perspective?

A. Yes, from the perspective of a person of ordinary skill in the art.
Q. And are the determinations that you have reached, were they reached from that perspective?
A. I made every attempt to do so.
Q. In the process of your work, did you attempt to define for the Court what you viewed to be the qualifications or the credentials of a person of ordinary skill in the art?
A. Yes, I did.
Q. And would you put slide 4 on, please? What are we looking at here, Doctor?
A. This is the definition of a person of ordinary skill in the art that was certainly in my first expert report and if it wasn't in my second or third, this was certainly referred back to at that point.
Q. Now, would you read it with the context being that you're pointing the Court to particular experiences or qualifications of that person, so read it, please, to the Court?
A. Yes. A person of ordinary skill in fields of biochemistry and immunology in 1994 would have had an advanced degree in a chemical or biological discipline and extensive experience in the synthesis, fractionation and characterization of polymers, such as their hydrodynamic and structural properties as applied to proteins, sympathetic peptides and/or polydispersed peptide mixtures, as well as experience in the determination of the

molecular weight distribution and average molecular weights of such polymers by methods such as size exclusion chromatography and an understanding of how the standards and the conditions used in the molecular weight determination affect the results obtained.

Q. That's a mouthful, but let me see if I can give the Court a little perspective on the issue by asking you to use the definition of person of ordinary skill in the art as Dr. Grant articulated it, and we have on the board his definition. The Court has seen this need not read it, but would you explain to the Court what if any material differences as you see it, there are in these two definitions?

A. They're quite similar. I guess perhaps I expect a little bit more of somebody of the ordinary skill in the art than Dr. Grant, but that's a matter of degree. In essence, you should pardon the expression, there's a great amount of overlap between the two definitions.

Q. All right, now, Dr. Grant indicated specifically that in his definition he would afford access to and the ability to consult with other scientists having related and/or complementary knowledge. How do you describe your statement in reference to that particular qualification?

A. Well, all scientists, research scientists take advantage of colleagues in areas that can complement their own area and it appears that Dr. Grant, as I, would do so.

Q. In other words, let me ask you the bottom line. Do you consider there to be from your point of view any material difference between these two definitions?
A. Well, as I mentioned, it's one of degree. I myself would probably have to consult less with others in areas of polymer chemistry and biochemistry and what I think he means by analytical chemistry than such a person of skill in the art, but again we're talking here of a person of ordinary skill. And in terms of somebody perhaps coming into my laboratory of ordinary skill, I guess perhaps I would expect perhaps a little bit stronger background in these areas, particularly since those are areas that were part of my research interest.
Q. And with that nuance, could you live with Dr. Grant's definition?
A. I have no problem with Dr. Grant, yes.
MR. SKILTON: With the Court's indulgence and your Honor when you've had enough of this, just I'll move on, but I would like to ask Dr. Zeigler to do a little teaching here on the biochemistry involved, so when the Court has enough, I assume you'll ask me to move on.
THE COURT: Okay.
Q. Dr. Zeigler, what is a peptide?
A. A peptide is a combination of two or more amino acids that are linked via a peptide bond or linkage.
Q. And then what is a polypeptide?

A. A polypeptide is a molecule that consists of many, many amino acids. Would you like me to give the classical definition of a polypeptide?
Q. Would you, please?
A. Originally a polypeptide was a peptide which would be retained in a dialysis sack in some sort of an aqueous solution.
Q. All right.
A. If it went through the dialysis sack, it was not a polypeptide. If it stayed there, it was.
Q. Thank you. And what is a polymer?
A. A polymer is a molecule made up of many building block units of some sort.
Q. And what is a copolymer?
A. A copolymer is a polymer made up of more than one different type of building block.
Q. What is a polydispersed mixture of polypeptides?
A. A polydispersed mixture of polypeptides is a mixture containing a range of sizes of polypeptides. It's polydispersed in that respect.
Q. Is a copolymer -- let me be even more specific. Is copolymer-1 as you understand that term has been used in this case a polydispersed mixture of polypeptides?
A. Yes, it is.
Q. And how, if at all, do polydispersed mixtures of

polypeptides differ from a protein?
A. A protein is either a single or a few related molecules. Let me explain that. Sometimes a protein will be bound to a substrate or something else, but in general, a protein is a single chemical entity.
Q. Dr. Zeigler, as we go through some of the relatively complex chemistry in your examination, where you feel it is necessary to differentiate as between these terms, please let me know and I'll ask you a proper question in that regard. Would you do that?
A. Fair enough.
Q. Let's turn, then, to your opinions. Have you reviewed the patents in suit?
A. Yes, I have.
Q. And have you reached opinions as to whether or not the asserted claims by Teva of the patents in suit are obvious?
A. Yes, I have.
Q. What is that opinion?
A. All of the claims in all of the patents in suit are obvious to one of ordinary skill in the art.
Q. And have you used in that analysis a date?
A. Yes, I have. That is the date of priority of the '808 patent, I believe it's April or May of 1994.
Q. Now, Doctor, as has been stated in this Court at various contexts, I think the lawyers certainly understand that issues

of obviousness are fixed questions of fact and law and for the Court. Have you in your opinions attempted to consider the law as it relates to obviousness?

A. Yes, I have. To a large extent, of course, I've depended on counsel because I make no claims for expertise in the law. But I've done the best that I can.

Q. And was that law that you were relying on in attempting to follow as a scientist part of your reports in this case?

A. Yes.

MR. SKILTON: Nick, would you pull up DTX 1954, please?

Q. This was data taken from one of the reports. The law you were following as indicated in this report is model patent jury instructions, I take it?

A. Yes.

MR. SKILTON: Nick, would you publish those portions that are in his report? More generally, Nick, could you publish it from the report itself, I believe it's DTX 1954, sorry. Your Honor, the Court is more than well aware of the law, so may I refer him to a specific part that he was following?

THE COURT: Sure.

MR. SKILTON: I have made a slide of a part of that and, Nick, now would you go to that slide, please? And it's now on this screen and the Court will note it's one of the

paragraphs from the model of jury selections.
Q. Dr. Zeigler, would you read that portion of law for the Court and into the record?
A. Surely. "Keep in mind that the existence of each and every element of the claimed invention in the prior art does not necessarily prove obviousness. Most if not all inventions rely on building blocks of prior art. In considering whether a claimed invention is obvious you may but are not required to find obviousness if you find that at the time of the claimed invention or the critical date there was a reason that would have prompted a person having ordinary skill in the field of the invention to combine the known elements in a way the claimed invention does, taking into account such factors as, 1, whether the claimed invention was merely the predictable result of using prior art elements according to the known function and, 2, whether the claimed invention provides an obvious solution to a known problem in the relevant field."
Q. And have you attempted to the best of your ability as a scientist to follow that construct in forming the opinions in this case?
A. I have.
Q. Now, I asked you about your assignment. Let me drill down a little more specifically. Have you prepared a slide that frames your assignment and the opinions that you're going to render in order to assist the Court to understand what you're

attempting to do?
A. Yes.
MR. SKILTON: Nick, would you please put the slide related to that issue up? Slide 7.
Q. Dr. Zeigler, would you go through this with the Court to frame the opinions that you're about to give?
A. Yes. From the perspective of a person of ordinary skill in the art as of the date of May 1994, I was requested to evaluate the following issues: One, whether the processes to make copolymer-1 claimed in the asserted claims in suit were taught by or obvious in view of U.S. patent No. 3849550, which will be referred to as the '550 patent, in combination with prior art. Two, whether the copolymer-1 products made by the processes claimed in the asserted claims were obvious. And, three, whether the uses of the copolymer-1 products in the asserted claims were obvious.
Q. All right. Dr. Zeigler, I want to take you to a particular construct and hypothetical, and for the next portion of your examination, to keep you within that hypothetical. So I will focus you on the date of May, 1994, and I think the Court recognizes the date of May 24, 1994 as the operative date for prior art questions. That's the date I'm asking you to use as the construct as a person of ordinary skill in the art and the knowledge that that person would have had as of that date.
And I want you in addition to that in answering these

questions and in developing your opinions to talk about art that would have been known to that person of ordinary skill in the art as of that date. Do you follow my request at this point?

A. I do. I would certainly think that the first place that, or the major, the primary place to look at would be the previous patent, which would have been patent '550.

Q. All right, now, let me finish the last tenet of my hypothetical. I want you in answering these questions to not refer to and disregard as a matter of the knowledge of that person of ordinary skill in the art whatever is taught or claimed in the patents in suit. Do you understand that as the framework of the hypothetical?

A. Yes.

Q. And so I want you then to take the Court through the art as of that date outside of the four corners of those patents. Where would you start if your goal was to make a copolymer-1 product?

A. Well, I would begin to look at the references at the end of the patents in suit. I'm sorry --

Q. Let me frame it, because I want you to answer the question without regard to the patents in suit.

A. Oh, without regard to the '808 patent, okay.

Q. I'm asking you hypothetically, you want to make copolymer-1 as of that date and the patents in suit are not tacked on the

board over your desk.
A. A-ha.
Q. Where would you start the process?
A. I would start the process in the literature, certainly in terms of polymerization of polypeptides.
Q. Is there any document in particular you would look to if you were attempting to develop a product for the treatment of multiple sclerosis?
A. Yes. I would look to the patentees and the laboratories in terms of seeing what they had done previously.
Q. And is there a patent that you would look to get to by that route?
A. Yes.
Q. And so what would you start with?
A. Well, I would start with the patents to see to what extent the literature and the prior knowledge was in terms of this particular group of patentees.
Q. Now, you mentioned the patent earlier, the patent that, for example, appears in one of your assignments is the '550 patent. Is that the patent that you were alluding to?
A. Yes.
MR. SKILTON: And Nick, may we have that PTX 26 published? Your Honor, this is, of course, in evidence already.
THE COURT: Yes.

Q. How would one read this patent in terms of the assignment of making copolymer-1?
A. One would first want to know to what extent the polymer had been made and described in patent '550.
MR. SKILTON: And turn, Nick, if you would, to column 2, lines 53 through 63.
Q. How does this inform that person of ordinary skill in the art in terms of how to make the copolymer-1?
A. The copolymer and its synthesis is discussed in this paragraph.
Q. And let's go through this paragraph sentence by sentence. The first sentence reads, "Copolymers according to the present invention are easily prepared by conventional procedures."
First of all, Doctor, does that sentence have meaning to you as a person of ordinary skill in the art?
A. Yes. It would mean that there basically is nothing new in terms of the present invention. That's essentially what I believe conventional procedures implies, indicates.
Q. And do you agree that copolymers described in the '550 patent are, quote, "easily prepared by conventional procedures," end quote?
A. Yes. We used and prepared and bought commercially some of these kinds of polymers, related polymers well before this patent was issued. That's obviously not from the position of somebody of ordinary skill, but the point was that some of them

were available commercially at the time and that could have been well known to somebody of ordinary skill.

Q. All right, now, let's continue through the paragraph and the procedures therein described and I'll point you to the next sentence which reads: "The first of the above copolymers was prepared from the N-carboxyanhydrides of tyrosine, alanine, gamma benzyl glutamate and EN" -- and you pronounce the word for me.

A. Epsilon N-trifluralinacetyllysine.

Q. Was this a procedure known in the art at the time?

A. Yes, it was.

Q. Is there any reference in particular that you might refer the Court to to illustrate that point?

A. Yes, there's a long review article that was published in Advances in Protein Chemistry a number of years before by Katchalski and Sela.

Q. Nick, would you pull up DTX 1783? Is this the reference that you're referring to?

A. Yes, I am.

Q. Nick, follow please to the first page of the text. Doctor, does this in fact describe such a synthesis this article?

A. This is a review article which discusses what has been done previously in the synthesis and chemical properties of poly a amino acids.

Q. What is the title of the article?

A. I just read it, essentially. Synthesis and Chemical Properties of Poly a amino acids.

Q. The two authors?

A. Ephraim Katchalski and Michael Sela.

Q. Is this a source known to persons of ordinary skill in the art at the time?

A. Yes, it was one of the most through review articles that was available at the present time?

MR. SKILTON: Your Honor, I move into evidence DTX 1783.

MR. JAMES: No objection.

THE COURT: Admitted.

(Defendant's Exhibit 1783 received in evidence)

Q. Let's go to some particular parts of this, Doctor. Go, if you would, to the table of contents. I'm going to refer you to II. How if at all does this inform that person in terms of the step that we were just addressing?

A. Well, the very first discussion of the review article after the introduction is the synthesis of poly a amino acids from N carboxy a amino acid anhydrides or NCA's.

Q. Does this follow the index, so to speak? It's page 248?

A. Yes.

Q. Nick, would you turn to that page in this publication? And highlight, if you will, the II Section. I'm going to point you, Doctor, to get through this examination quickly to a

paragraph I want you to look at and comment for the Court. It begins with "although" on the second paragraph.

A. "Although a number of different derivatives of alpha amino acids and peptides have been used as monomers for the preparation of poly a amino acids, the most suitable and commonly used are the N carboxy a amino acid anhydrides."

Q. How does this teach a person in reference to the step you just looked at?

A. That it's a pretty conventional procedure.

Q. Nick, please return to PTX 26, the '550 patent and again, to column 2, lines 53 to 62. All right, we're on the process as disclosed and Dr. Zeigler, had you prepared a video to illustrate the process that is disclosed in the '550 patent?

A. Yes, I have.

MR. SKILTON: With the Court's permission I'd like him to play video 1.

Q. Doctor, I'm going to ask you and perhaps you can help me here. First of all, we're looking, are we not, to the '550 patent on the screen?

A. Yes, we are.

Q. And description of that patent. Take us in, Nick to the video and, Doctor, I'm going to ask you to stop me or point to the Court -- again, we're seeing the procedure that you just identified. This is a step, the steps that we're talking about now highlighted, including the sentence of depolymerization.

Nick, would you go back to the last slide? Sorry, your Honor. I want the -- read the sentence into the record, the polymerization?

A. Yes. "The first of the above copolymers was prepared by the N carboxyanhydrides of tyrosine, alanine, gamma benzyl glutamate and Epsilon N-trifluralinacetyllysine. The polymerization was carried out at ambient temperature in anhydrous dioxane with diethylamine as initiator."

Q. Proceed, if you would, to the demonstrative?

A. The beginning of the demonstrative was the same as Dr. Kent showed, but as we'll see the emphasis here is quite different and it will diverge shortly.

So this is a solution representing the solution of polymerization. Again, Nick, if you can hold this for a second please. This part here again was shown yesterday so I'm not going to dwell too much on it. But alanine is represented in the red; glutamic acid, which has got this side chain of gamma benzyl group by the coral color; lysine, which is protected by the Epsilon N trifluoroacetyl group is in the purple and tyrosine here is in the green. The reason for the shape is to show the head-to-tail polymerization via the peptide bond.

Q. Now, as we were looking at the '550, I'm going to review the steps disclosed and as you narrate this video, if you would point the Court to how any or all of these steps are illustrated.

The first reads as follows: The first of the above copolymers was prepared from the N carboxy, etc. We've been through that step several times. Is that step illustrated in what we've seen so far?

A. Yes. These are all represented as the N carboxyanhydrides of each of these four amino acids.

Q. And the next clause of that same description reads, "The polymerization was carried out at ambient temperatures in anhydrous dioxane with diethylamine as an initiator." However you say it. What assumptions are you making in reference to those subjects?

A. Well, for one thing, one needs a trigger to begin the polymerization and that's what the role of the initiator is. And for another thing, as Dr. Kent mentioned, one wants to avoid reactions from the side chains and therefore two of these amino acids have got reactive side chains and must be protected.

Q. And the next clause reads, "The deblocking of the gamma carboxyl group of the glutamic acid was affected with hydrogen bromide in glacial acetic acid." Doctor, keep going through the video and illustrate or point out to the Court how we're attempting to show that.

A. First we're going to go through the polymerization. Again, this is in common with what Dr. Kent showed yesterday and I'm not going to repeat what he said in detail, but this is the

polymerization reaction, and one can see, once one adds initiator to start, that there's a section in which the first beginning chain is going to start to be polymerized. This is supposed to represent a random polymerization, but at the same time that that group was forming and was fairly large, a new chain is beginning to start, and one could see here is that as the N carboxyanhydrides are beginning to be used up different chains are beginning to start through the solution and this is going to be at least partly or mainly the basis of the polydiversity that one gets at the end of the reaction.

Again, one can see that the peptides that is the glutamics have got the gamma benzyl group and the lysines have got the trifluoroacetyl groups on them. So this is the fully protected copolymer-1.

Q. Now, the last clause of that portion reads, "And was followed by the removal of the trifluoroacetyl groups from the lysine residues by one millimeter piperidine"?

A. First of all, we didn't talk about the next step. The next step is actually treatment with HBr and acetic acid. The gamma benzyl groups are removed first and that's going to be shown here in this inset which comes from this section of the slide and focus in on the glycines. The glycine is going to have the gamma benzyl group removed once this treatment occurs, and this is going to occur throughout the treatment of this solution, and result in the trifluoroacetyl protected copolymer-1.

Nick, could you hold this for us to continue?

So now to answer the question, yes, this was followed by the removal of the trifluoroacetyl groups from the lysine residues by 1 molar piperidine in order to give the copolymer-1 itself and this is going to be the last part of the demonstrative.

Q. Could you follow? Thanks. All right, now take us through this slowly.

A. Yes. Again, here is the section that's being magnified and we're going to add this piperidine which is going to be removed -- I'm sorry, which is going to result in the removal of the epsilon N trifluoroacetyl groups. And at this point here we have copolymer-1 produced.

Q. Pursuant to the method disclosed?

A. Yes.

MR. SKILTON: Your Honor, I'm sorry to have a lozenge in my mouth. I'm doing it for my throat.

THE COURT: That's okay.

Q. Now, does the recitation in that portion of the '550 patent that we've now gone over provide that person of ordinary skill in the art with the experimental details that he would need specifically?

A. No. The experimental details for the most part are left out.

Q. Now, is there anything in that '550 patent to refer the

person to a source or specifics as they may relate to the experimental details?

A. Yes, there's a reference at the end of the patent to the patentees.

MR. SKILTON: Nick, would you turn again to PTX 26 and column 4, lines 30 through 32.

Q. What are we looking at here?

A. We're looking at a reference to Teitelbaum, et al, European Journal of Immunology, 1971.

Q. And so would that person of ordinary skill follow the trail to that reference?

A. Yes.

MR. SKILTON: Nick, would you please pull up PTX 499? And, your Honor, I believe this is also in evidence.

Q. What are we looking at here, Doctor?

A. We're looking here at an article by Drs. Teitelbaum, Meshorer, Hirshfeld, Arnon and Sela. The title is Suppression of Experimental Allergic Encephalomyelitis, or EAE, by a Synthetic Polypeptide.

Q. Is this the 1971 Teitelbaum article that was specifically referenced in the '550 patent?

A. It is.

Q. And of course Teitelbaum along with Drs. Arnon and Sela were amongst the inventors of the '550 patent, is that correct?

A. That is correct.

Q. Now, where in that article are additional experimental details disclosed to that person of ordinary skill in the art?

MR. SKILTON: Nick, would you look at page 243? All right.

Q. What are we looking at here?

A. This is in the experimental methods section, and the 2.3 discusses the Katchalski and Sela article, and 2.3.1 --

Q. That's the one you earlier reviewed?

A. Yes. 2.3.1 discusses copolymer-1 particularly and gives a little bit more detail than the patent itself.

Q. Do you know whether this is the same procedure that's described in 2.3.1, the same procedure as described in the '550 patent?

A. Yes. It must be because that's what they refer to in patent '550.

Q. Now, have you prepared a demonstrative to aid on discussion of this procedure?

A. Yes.

MR. SKILTON: Nick, would you turn to slide 8, please? Thank you.

Q. What is it that we're looking at here in slide 8?

A. We're looking at a comparison of the language of the '550 patent to the language that you had pointed us to in the method section of the Teitelbaum 1971 paper.

Q. And it's a side-by-side comparison of the processes as

described respectively?
A. Yes.
Q. Are there additional references or citations in the Teitelbaum 1971 description that would be significant to the person of ordinary skill in the art?
A. Yes. In particular, one would like to see the conditions of deblocking of the gamma carboxy group and conditions for the removal of the trifluoroacetyl groups from the lysine residues.
Q. Why would this particular portion of the experiment be of particular interest to that person of ordinary skill in the art?
A. Because one has to know the conditions under which they're applied.
Q. Is there a reference cited by the Teitelbaum article?
A. For which one, Mr. Skilton?
Q. Let's be as specific as I can be.
MR. SKILTON: Nick, would you call up page PTX -- I'm sorry, let me start again.
Q. Is the Ben-Ishai Berger reference a part of that description in the Teitelbaum article?
A. Yes. If you look at the references, reference 16 refers to the Ben-Ishai and Berger article.
MR. SKILTON: Nick, would you pull up, please, the footnote 16 so the Court can follow the trail here? Where is that shown in 16?

Q. There's the reference. And how does that question then relate to the questions you were addressing in terms of that step?
A. That reference is going to give the conditions for hydrogen bromide deprotection of the gamma benzyl glutamate.
Q. And so would the person of ordinary skill in the art then look to this article to try to ascertain the conditions?
A. Yes, absolutely.
MR. SKILTON: Nick, would you pull up PTX 499, please?
Q. We're looking at what here, Doctor?
A. The Journal of Organic Chemistry. 1952.
Q. 1952. Is there a particular article in there, then, that you're looking for?
A. I assume it's the Ben-Ishai and Berger.
Q. Would you turn to that article, Nick? Is this the article that's referenced in the Teitelbaum 1971 paper?
A. Yes, it is.
Q. Where does it appear, what's the journal it's in?
A. Journal of Organic Chemistry.
Q. Is this a journal you relied on in forming your opinions in this case?
A. It is.
Q. And you're familiar with the content?
A. I am.
Q. And the journal is a reputable journal?

A. It's one of the premier journals in the field.

MR. SKILTON: Your Honor, I move into evidence Exhibit 499.

MR. JAMES: I think you misspoke. I don't think that's what you intended to say. 499 is in evidence.

MR. SKILTON: I'm not following my notes correctly, I'm sorry. Is this Exhibit 1799 that we're looking at? Excuse me, your Honor.

THE COURT: That's all right.

MR. SKILTON: Is this Exhibit 1759 that we're looking at?

MR. JAMES: We have no objection, your Honor.

MR. SKILTON: Thank you.

THE COURT: All right, admitted.

(Defendant's Exhibit DTX 1759 received in evidence)

MR. SKILTON: Forgive the incompetence of the examiner.

Q. Doctor, as you look at Exhibit 1759 in particular the article by Ben-Ishai and Berger. How would a person make use of the information in this article here doing the experiment recited in the 1971 Teitelbaum article?

A. He would look inside to find where the description of gammic benzyl, gamma benzyl deprotection is described.

Q. We started that process. Let's go, if you would, to the exhibit specifically, and I want to direct your attention to

page 1566. And there is a statement in the article on that page concerning benzyl esters. Would you read that, please, into the record?

A. Yes. Let me first explain the word "also." This article covered the deprotection, the deprotection of two groups simultaneously, and it focused on the other group which has no relevance to the case. I just want to explain the word "also."

"Since benzyl esters are also cleaved by hydrogen bromide in glacial acetic acid, but under more stringent conditions than N carbobenzoxy groups. Benzyl hippurate prepared by benzoylation of glycine benzyl ester gave hippuric acid a treatment with hydrogen bromide in glacial acetic acid for 12 hours."

Q. Do Ben-Ishai and Berger and in particular in the portion that you're looking at describe deblocking glutamic acid with hydrogen bromide in glacial acetic acid?

A. Yes, they do.

Q. And I see that benzyl ester is used in the experiment and in this one. What is benzyl ester?

A. Well, benzyl ester is a group that's utilized by peptide chemists to protect, that is to deactivate reactive groups, by peptide chemists on peptides.

Q. Are benzyl esters used in the process of preparing copolymer-1 that is described in the '550 patent?

A. Yes.

Q. Now, the word protecting group has come up in your descriptions. Is that a form of the reaction that we're looking at, is that relating to protecting groups at all?
A. Yes, it is. It's essentially the same thing and in these particular cases are also cleaved.
Q. Is this the same protecting group used in the patents in suit for glutamic acid?
A. Yes, it is.
Q. Do Ben-Ishai and Berger describe the experimental conditions under which this deblocking or deprotection occurred?
A. Yes, there's a section at which they describe it in more detail.
Q. Nick, would you turn to page 1566? And I'll ask you, are experimental conditions for deprotection of glutamic acid described on this page?
A. Yes, it is.
Q. And show the Court what you're referring to and explain to the Court how this section relates to that question.
A. Right. Now benzyl hippurate is related to amino acid not to a peptide. This is the very first paper in the field of HBr in glacial acetic acid being used to block or deprotect or cleave benzyl esters, and so this is a relatively simple system. It reads, "To benzyl hippurate there was added hydrogen bromide in glacial acetic acid and the mixture was

left overnight at room temperature." Which was interesting, because in the text it said 12 hours at room temperature.
Q. All right. And let me elaborate a little bit on what you said. Move on in the paragraph. Is there any reference to the time here of the reaction?
A. Yes. The time here is overnight. Earlier it said 12 hours.
Q. And how do you interpret overnight as a person of ordinary skill in the art? What is being denoted there?
A. It denotes how hard you work in the laboratory. If you leave at 6:00, so it's 16 hours, 17 hours. If you leave at 10:00 or 9:00, say, it would then be twelve hours.
Q. So what is disclosed here with respect to this element of time with respect to the deprotection of glutamic acid in this experiment?
A. Time and temperature are important parameters dealing with chemical reaction in general, and in particular, that's what's reported here for this particular material.
Q. And show specifically where temperature in that condition is reported in this reference.
A. At the very end it says "at room temperature".
Q. What does that mean?
A. I've been in Israel and I know that the laboratories can be as cold as 12 degrees -- I'm sorry, as 20 degrees centigrade and as warm at 28 degrees centigrade. I assume what that meant

it was done at the lab, it depends on the time of day and depends on the temperature in the laboratory.

Q. Following the trail, then, that the '550 put you on --

THE COURT: Mr. Skilton, I'm sorry to interrupt you. I have a matter that's going to require about ten minutes of my time, so we'll have to adjourn.

MR. SKILTON: Yes, your Honor. Thank you.

THE COURT: Be back in ten.

(Recess)

(In open court after the recess)

THE DEPUTY CLERK: All rise.

THE COURT: Please be seated.

All right, Mr. Skilton, you may proceed.

MR. SKILTON: Thank you, your Honor.

Q. Dr. Zeiger, we've been going through fairly complex, some might call it dense, others boring, articles on chemistry here, but let me see if I can focus on the point. And we've been through the '550 patent up to the last sentence.

So, Nick, would you please put slide eight back on the board for the Court, and I'm going to ask you right up to the last sentence, the sentence that relates to the lysine residues. What have you, as a person of ordinary skill in the art, seen as a result of whether or not the procedures disclosed up to that point were conventional procedures as stated in the '550 patent?

A. They're conventional, though certainly routine to a person of ordinary skill in a peptide chemistry laboratory.

Q. And what you've done, essentially, is to, if you will, trace the patent through some of the resources that would be available to that person of ordinary skill, is that correct?

A. That is correct.

Q. And showing where those steps essentially are reported in the art?

A. Yes.

Q. Now, let me take you to the last sentence of that, and it may be the place, and it says "What's followed by the removal of the, and would you --

A. Trifluoracetyl groups.

Q. Thank you -- from the lysine residues by 1 millimeter piperidine?

A. 1 molar, I'm sorry.

Q. Molar?

A. 1 molar, piperidine.

Q. You will continually remind me I'm a history major.

A. I don't mean to correct you.

Q. Is that a step that was a conventional procedure as well?

A. It was, especially Anfinsen's laboratory.

Q. And what do you mean by that?

A. The authors of the original treatment included Chris Anfinsen.

Q. And are you referring here to DTX-1711?

A. Yes, I believe so. That's the also reference 17 of the Teitelbaum paper.

Q. All right. And, Nick, if you pulled that -- yes, you have up on the board.

Are we now looking at an article, and its title is what, please?

A. Reversible masking of amino groups in ribonuclease and its possible usefulness in the synthesis of the protein.

Q. And the authors are?
A. Robert Goldberger and Christian Anfinsen.
Q. And the date of receipt is?
A. February 7th, 1962.
Q. And the publication is?
A. I believe the Journal of American Chemical Society, but --
Q. Is that --
A. Oh, I'm sorry, it's Biochemistry.
Q. Is this a reputable source?
A. Yes, it is.
Q. Is this an article that you relied on in forming your opinions in this case?
A. Yes.
MR. SKILTON: Your Honor, I move into evidence DTX-1711.
MR. JAMES: No objection.
THE COURT: Admitted.
(Defendant's Exhibit 1711 received in evidence)
Q. Now, does this reference teach the step that we just described, to wit, stopping the reaction in the presence of acetic acid?
A. It does.
Q. And without going into the detail of it, that information would be found by a person of ordinary skill in the art reading the article, correct?

A. Yes.
Q. I'll take you back to the slide, Nick, please, comparing '550 to Teitelbaum, thank you.
Is it your opinion that a person of ordinary skill would find the process for preparing copolymer-1, as that process is described in Teitelbaum 1971, to be well known?
A. Would you please repeat the question?
Q. Yes, I will. Is it your opinion that a person of ordinary skill would find the process for preparing copolymer-1, as that process is described in Teitelbaum 1971, to be well known?
A. Yes.
Q. Is it also your opinion that a person of ordinary skill would find the process for preparing copolymer-1, as that process is described, is also described in the '550 patent, to be well known?
A. Yes. Assuming that one follows the literature trail that we have gone through.
Q. Now, Nick, would you please put back on the board PTX-26.
And I now want to focus your attention and the Court's attention on the nature of the product that are produced by the process disclosed in the '550 patent. And let me direct you to lines 57 through 68 of the '550 patent. And would you read the sentence beginning -- let me read it and make this quicker. I'm going to refer you to that portion of this paragraph that reads as follows from line 61. "The molecular weight of the

copolymer being in excess of 10,000 and preferably above about 18,000, and the copolymer being characterized by a net positive electrical charge and by a content of a lesser quantity of a negative electrical charge."

What does this paragraph, this sentence tell the person of ordinary skill in the art about the nature of the products that are produced by this process?

A. Certainly, there's a poly dispersity that's disclosed, in other words, an excess of 10,000 would at one point, and preferably above about 18,000 and at another point, this would support the whole idea of poly dispersity in terms of expectations on the part of a person of ordinary skill. And the latter part there indicates that there is a wealth of positive charged side chains and lesser wealth of negative negatively charged side chains.

Q. And does the '550 patent direct that person of ordinary skill in the art to a preferred range?

A. It says above 18,000 daltons.

Q. Are there other ranges or molecular weights disclosed in the four corners of the '550 patent?

A. Yes, there are other numbers that are mentioned either in the specifications or the claims.

Q. Let's see if we can spot some of them.

A. Okay.

Q. Nick, would you turn to column three, line 28, please?

A. Could I just -- should I wait for that to be highlighted or --

Q. Well, it probably will make it go faster because I think we've talked about this before.

A. At 15,000 and 25,000 molecular weights are also indicated, that is a claim.

Q. And how about column two, line 22? Let's highlight that and explain it to the Court?

A. Again, this is the beginning specifications. It talks about a molecular weight of about 20,000 to 25,000. So there are a host of different molecular weights that are referred to in the patent '550.

Q. Now, what do these disclosures in combination say about the molecular weight of the copolymer-1 product as taught by the '550 patent?

A. That there is batch-to-batch variation in terms of the molecular weight distribution, that is different size range of the products, namely, copolymer-1.

Q. And with respect to molecular weight, does it teach the weight ranges that one could expect to get by following this process?

A. Well, the lower range that it mentioned is in excess of 10,000, and the upper range it mentions is 25,000. As I just pointed out, there are several numbers in between as well.

Q. All right. Now, I'm asking you here to apply your

knowledge and the experience of a person of ordinary skill in the art to the disclosures that are therein made as you now described.

Is it fair to say that the '550 patent teaches a range of molecular weights from in excess of 10,000 to 25,000?

A. I think that's fair.

Q. And I'm going to take you outside now of your hypothetical to the '808 patent; for example, one of the patents in suit. How do these ranges, those ranges that are expressly disclosed in the '550 patent, compare to the ranges disclosed in the '808 patent?

A. The ranges in the '808 and patent and patents in suit are lower than 10,000.

Q. All right, so let's take that as a framework, and as you read the '550, take you out of the '808 back to the hypothetical, where you're not considering disclosures of the '808, does the '550 patent teach the production of copolymer-1 in the range of 15 to 20?

A. Yes, it does.

Q. And does it teach the production of copolymer-1 in the range of ten to 15?

A. Yes.

Q. And as we established, it teaches a preferred range, correct?

A. That's what it says, yes.

Q. And from your reading of the patent, that preferred range is what?
A. About or above 18,000.
Q. Now, let's assume that the person of ordinary skill in the art, realizing the range variations that are disclosed in the '550 patent, wants to produce within the preferred range, the copolymer-1 product. Do you have that assumption?
A. Yes.
Q. How does that person of ordinary skill in the art approach the disclosures of the process in the '550 patent to produce to the preferred range, what are the factors -- what does he look at?
A. Well, the polymerization, as I mentioned, is going to give some batch-to-batch variability in terms of the molecular weight. The fact that the preferred range is above 18,000 would indicate that that's what the patentees are shooting for, but, nonetheless, they fully acknowledge that they may get something as low as in excess of 10,000.
Q. And so if your goal was to produce within the preferred range, what are the experimental condition variabilities, if any, that you would look to as that person of ordinary skill in the ordinary?
A. One would try to eliminate any kinds of cleavage or of termination of the polymerization.
Q. And is there a particular step of the patent that you would

look to in terms of elimination of cleavage, as you've just stated?

A. Well, elimination of cleavage, as I mentioned, there's some aspects in terms of the synthesis of the copolymer. But, in addition, one might suspect that acid can cause peptide bond cleavage as well.

And the reason I believe Dr. Kent mentioned that amino acid yesterday, that amino acid analysis was done under conditions of strong acid. And this is not only my opinion, but we'll see in the literature, perhaps later on this morning, that this opinion is shared by others in the field.

Q. All right. Now, you mentioned a step in the patent and you mentioned acid. In this disclosure, the '550 patent, what step are you referring to in giving the answer you just gave?

A. Well, the acetic step is HBr and glacial acetic acid in terms of the potential for peptide bond cleavage.

Q. And why, in trying to ascertain how to, if you will, work the experiment to come to the preferred range, why would the person of ordinary skill in the art look to that step?

A. Well, as I mentioned, that's a step which involves strong acid, and the classical conditions utilized strong acid, in fact a weaker acid, if you will, with HBr would, for the most part, HCL, HBr certainly could do it.

Q. Now, explain the chemical mechanism that that person of ordinary skill in the art would be looking at as he looked at

this HBr step, what is it that he's looking for here, Doctor?
A. He would be looking for evidence of cleavage of the peptides to a lower molecular weight range.
Q. All right. And here you have to tell the Court what you mean by cleavage of the peptide bond. What are you referring to and why are you pointing to this as part of the '550 process as disclosed?
A. If I can answer the latter part first. The latter discloses a broad range of expected sizes and distributions of peptides.

As for the first part of it, if I'm understanding correctly, I can illustrate it by, for example, thinking of a single poly -- a single polypeptide molecule of 20,000. If it should happen to have been broken exactly inbetween, it would result in two molecules of 10,000 molecular weight. In other words, cleavage breaks materials into at least two fragments and lowers the size of the molecular weight of the products.
Q. Now, have you prepared and worked on a video to try to illustrate the chemistry and the reaction that you have described in words?
A. I have.
Q. And, Nick, would you go to that video, please. And, Doctor, here rather than me interrupting you on occasion erroneously, would you narrate this for the Court to maximize the demonstration of the point you're trying to make and work

with Nick in the process?
A. Yes. This is where, at least one place where the demonstrative, the animation differs from that of Dr. Kent, yes. This is going to discuss the deprotection of peptide cleavage by HBr.
Could you run the demonstrative? So this is -- you'll recognizes the fully protected copolymer-1. And now we're going to have HBr treatment acetic acid. Again, we're going to illustrate a small fraction of this.
And over here is the removal of the benzyl group, but now occasionally what's going to happen, potentially, is acid cleavage at the glutamic acid residues. So this is going to happen on occasion if, in fact, there is a cleavage of the peptide chains. And one can see this happening throughout the solution, larger peptides breaking up into smaller peptides.
Q. Now, how does this cleavage phenomenon that you've described in this illustration affect this issue of molecular weight variation as the person of ordinary skill in the art would understand it?
A. It would take a material, a relatively higher molecular weight to a product of relatively lower molecular weight.
Q. And why is that?
A. As I mentioned, any time you break up a fragment or peptide into fragments, the fragments are lower molecular weight in fact add up to the original fragment size.

Q. Now, is this word "cleavage" expressly discussed in the '550 patent?
A. No, it is not.
Q. Is the term "peptide bond cleavage" expressly discussed in the '550 patent?
A. No, it is not.
Q. And explain to the Court, if you would, how would a person of ordinary skill in the art circa May 24th, 1994, with the knowledge then available to that person, know that HBr cleavage was responsible for this reduction in molecular weight?
A. As I mentioned, he would, he would suspect this is a possibility for some of the or all of the variation. And he would, as we say, he followed the paper trail, the paper trail leading to the people publishing HBr deprotection, namely, Ben Shine & Berger.
Q. This is the same paper trail that we were already on, correct?
A. Well, this was reference 16 of the Teitelbaum paper discussing the conditions for HBr cleavage of gamma benzyl-esters. Now, that was not done with peptides, that was done only with amino acids. And, consequently, one might expect that a laboratory interested in HBr cleavage might go to a more complex mixture.
Q. All right. And take the Court through what you are positing is the thought process of that person of ordinary

skill in the art as he evaluates the molecular weight range variation of the '550 and looks for an explanation of it?
A. A person of ordinary skill coming into my laboratory would be expected to go back to the areas, the laboratories that were interested in the subject, and to be able to follow what they have done subsequently with that reaction.
Q. All right. And earlier in your testimony following the trail, you mentioned -- and we have put into evidence, the Ben-Ishai and Berger publication.

State, if you will, how that publication leads -- where and how that publication leads to a person of ordinary skill in the art to other art in the field?
A. Well, Arieh Berger was the head of the laboratory at that laboratory at the Weizmann Institute, and I would look to subsequent publications from that, that laboratory first. It doesn't mean it has to be there, but, again, the interest was there. And that would be the way I would expect a person of ordinary skill to pursue the question.
Q. And following that lead, so to speak, Doctor, is there a reference that you want to now point out to the Court and describe to the Court?
A. Yes, there is, from the same laboratory.
Q. All right. And, Nick, would you pull up DTX-1934.

Doctor, first would you state what is the title of this article?

A. Multi chain poly amino acids containing glutamic acid, aspartic acid and proline.
Q. And the authors?
A. Arieh Yaron and Arieh Berger.
Q. And the department that they're working with?
A. The Department of Biophysics where I spent two years on my sabbatical.
Q. And the date of the article?
A. Received January 29th, 1965.
Q. And where is it published?
A. Biochemica at Biophysica Acda.
Q. Is that a reputable source to scientists in the field?
A. Yes, it is.
Q. And is this an article that you relied on in forming the opinions that you have arrived in this case?
A. Yes, it is.
MR. SKILTON: Your Honor, I move into evidence DTX-1934?
MR. JAMES: No objection.
THE COURT: Admitted.
(Defendant's Exhibit 1934 received in evidence)
Q. This is the same Berger as the Berger whose work was referenced in the Teitelbaum article?
A. Yes, it is.
Q. Now, where in this article -- let's call this the Yaron and

Berger article -- is there any discussion of peptide cleavage by HBr?

And to facilitate and speed up this, Nick, would you turn to pages 317 through 318?

And, Doctor, I'm going to point your attention to particular portion of this paragraph that have been highlighted, and I want you to relate those portions to the issue of what these sentences disclosed to that person of ordinary skill in the art with reference to cleavage of the peptide bond?

A. This paper is concerned with peptides, and it's a later paper, 13 years after the first one. And as the sentences read, as indicated by previous investigations, reference 21, debenzylation by means of hydrogen bromide and in glacial acetic acid may lead to some degradation of peptide bonds. Conditions of debenzylation were, therefore, sought under which this degradation is minimal.

In the case of multi chain polymers, such as multi chain poly glutamic acid where side chains of poly glutamic acid are attached to a poly lysine back bone, degradation of the side chains can easily be detected by chemical analysis.

Q. All right. Now, let's focus on what's been stated. First of all, what is debenzylation?

A. The removal of benzyl groups.

Q. And is this a process also referred to as deprotecting or

deblocking by that person of ordinary skill in the art?
A. Yes, it is.
Q. And what would, what would the person of ordinary skill in the art be able to take out of this paragraph?
A. They, the authors Yaron and Berger, are clearly convinced that there is some degradation of peptide bonds that could occur by HBr and glacial acetic acid treatment, and they refer to an earlier publication as their basis.
Q. And what is the significance of this conclusion and/or disclosure of Yaron and Berger as it relates to the process described in the '550 patent for preparing copolymer-1?
A. Yes. If you want to avoid peptide cleavage, you better find conditions in which peptide cleavage does not occur.
Q. And so is it fair to say that in this particular experiment, Yaron and Berger were seeking conditions to prevent cleavage?
A. Yes. They say so directly.
Q. And how does, if you will, that particular goal in that experiment convert to information or knowledge that would be relevant to that person of ordinary skill in the art working the '550 experiment?
A. Well, any person of ordinary skill that knows chemistry knows that two of the main parameters of a chemical reaction are temperature and time.
Q. Now, how did Yaron and Berger, the article we're looking

at, go about determining the conditions in this case to prevent cleavage from occurring?

A. Well, there's a paragraph that's coming up, which discusses this.

Q. And do we have that, page 318?

A. Yes, it's on the board.

Q. It's the paragraph that starts, optimal conditions.

And, Nick, would you highlight that through the sentence that begins the absence.

Now, Doctor, I don't think the Court needs to know the particular chemistry of this portion, but would you explain how this is relevant to the question of peptide bond cleavage and the person of ordinary skill in the art worrying about the ranges that are produced by the '550 process?

A. Yes. What they mean by optimal conditions is that they mean conditions in which they get 100 percent deprotection, and at the same time get zero peptide bond cleavage. That's what they're referring to there.

And at the end of the second sentence, it says that they achieved this or at least they say that for glutamic acid glatiramer derivatives, three days of treatment at 2 degrees Centigrade was necessary. And under these conditions, no degradation of the side chains could be detected by quantitative amino acid analysis after prolonged dialysis.

Now let me explain here about side chains. The side

chains are peptides themselves, and therefore, we're not talking about debenzylation. We're talking about peptide bond cleavage. Is that clear?

Q. Well, it is to you, but let me ask the question. What variables here are being adjusted to control in this case the amount of cleavage, what are they looking in particular?

A. They're looking at time and temperature in order to differentiate benzyl-ester deprotection from peptide bond cleavage.

Q. And here I would like you to be a little bit specific for the Court. Where is the time variation noted in this paragraph and where is the temperature?

A. In the second sentence it talks about the glutamyl residues in these so-called side, and that's what multi chain polymer is, I don't want to get into this now if I don't have to, but --

Q. Don't. Move on.

A. But under these conditions, they were able to get 100 percent deprotection of benzyl groups and avoid peptide bond cleavage by hydrogen bromide.

Q. Now, are these experimental variables to control cleavage amount, time and temperature, are these variables that you would characterize as being variables that would be known in terms of their manipulation to the person of ordinary skill in the art?

A. Certainly as I've defined it, yes.
Q. And they are parameters that can be adjusted, is that a fair characterization?
A. Yes. And I would expect somebody of ordinary skill in terms of peptide chemistry, to realize this; that just as one can lower the temperature to avoid something, one can utilize this as a tool for his chemical tool box. It's one of the arrows in his arsenal.
Q. Would you go so far as to call them routine parameters?
A. The parameters are routine.
Q. And they would be in what you just characterized as that person in the lab's tool box?
A. Well, the tool box should be -- the temperature and time can be varied. In one case you can avoid something, and in the other case you can accelerate it.
Q. Now, what does the disclosure, as you're describing and have characterized in this publication, Yaron and Berger publication, indicate as to what would occur under the conditions cited in Teitelbaum's 1971 for the HBr step?
A. Well, it indicates that Yaron and Berger fully would have expected such cleavage to occur. And that's based on a citation that was shown earlier.
Q. All right. Now, take it, if you could, to, I'm going to say that step. Was there a debenzylation and peptide cleavage occurring under the conditions stated in the '550 patent?

A. According to the statement in Yaron and Berger, I would come to the conclusion as a person of ordinary skill that it was most likely to have occurred.
Q. And using that disclosure in combination to the steps disclosed in the patent and the weight ranges given, would that person of ordinary skill in the art, knowing the HBr cleavage potential, be given information that would permit him or her in that lab to control the production of copolymer-1 within the various ranges that you've described?
A. Mr. Skilton, I would expect him first to do a more thorough investigation of the literature to be -- before coming to that conclusion, but that would certainly be the beginning of the start of the process of coming to a scientifically acceptable conclusion that HBr cleavage under these conditions is likely.
Q. All right. Now, you indicated you expect that person to go further. Does the Yaron and Berger article give that person a clue as to where to go?
A. Yes.
Q. And, Nick, would you turn to page 13 -- 331, sorry, 331. And particularly refer you to footnote 21.
Doctor, what are we seeing here?
A. This is a reference to a paper by Idleson and Blout in the Journal of American Chemical Society, 1958.
Q. And is that article one that you have also looked at in conjunction with the work that you've done in this case?

A. Yes it is.
Q. And, is that article in fact what DTX-1855 is?
And, Nick, would you pull it up?
A. That's certainly the journal, and that's the year, and that's the article.
Q. All right. Well let's go back and mark it and get it in the record first. What is the journal that this is published in?
A. The Journal of the American Chemical Society.
Q. And the date of publication?
A. 1958.
Q. And is this a reputable society?
A. Yes, it is. It's probably the --
Q. Is it --
A. -- premier journal for chemists.
Q. All right. And does the article that was referenced in the earlier publication appear within this journal?
A. Yes.
Q. And it is the Idleson and Blout. And would you please read in the title of the article that you're going to be commenting on?
A. High molecular weight, poly alpha L glutamic acid. That will be abbreviated in the article as PGA, so if we can just keep that in mind -- preparation and optical rotation changes.
Q. And the authors?

A. Idleson and Blout?
Q. And the date of publication?
A. January 31st, 1958.
Q. Is this an article that you have relied on in forming your opinions in the case?
A. Yes, it is.
MR. SKILTON: Move it into evidence, your Honor.
MR. JAMES: No objection.
THE COURT: Admitted.
(Defendant's Exhibit 1855 received in evidence)
Q. All right, now take the Court through this article in its relevant disclosures, Doctor.
Would you, Nick, turn to page 4632. And I'm interested in the paragraph that begins, it was originally thought. Can you find that?
A. It's at the lower, begins at the --
Q. It's a split.
A. Yes.
Q. They are clever, aren't they.
Okay. I've referred you here to a particular paragraph. Doctor, would you point to those portions of that paragraph that have relevance to what you're going to explain next?
A. If you recall, I mentioned that strong acid was responsible or was a classical means of hydrolyzing peptides to the amino

acids, and that was probably the basis for the statement. Certainly the statement is very clear cut.

It was originally thought that in the presence of HBr, traces of water would cause cleavage of peptide bonds. Accordingly, considerable effort was expended to obtain completely and hydrous conditions. However, subsequent experiments showed that small amounts of water did not decrease the molecular weight of the final products.

But the key here is the next paragraph. And again Idelson and Blout's motivation is to avoid peptide cleavage in their reaction. And that's why they say that hydrogen bromide in glacial acetic acid has not been found to be a useful reagent solvent there for the preparation of LPGA, that is poly el-glutamic acid -- because, and I want to emphasize the part B, lower molecular weight LPBG's is a poly benzo glutamate -- show extensive peptide bond cleavage.

Q. What does this paragraph or plural, paragraphs, teach the person of ordinary skill in the art with respect to the use of HBr in glacial acetic acid?

A. HBr glacial acetic acid certainly has the capability of causing peptide bond cleavage when benzyl glutamic acids are treated with it.

Q. Now, how does this article or these disclosures inform or teach the person following the '550 patent as to conditions for deprotection of glutamic acid?

A. Well, certainly the idea of using temperature and time has already been introduced by Yaron and Berger. The conditions are discussed in the methods.

But the statement I think is pretty clear, that lower molecular weight LPGs shows extensive peptide bond cleavage. There's a whole table there, which I'm not going to go into.

Q. Okay. Well, without being too detailed, let me see if I can get to the heart of it.

Does this show cleavage of glutamic acids under various time and temperature variations?

A. In a number of different solvents and conditions were used and the ability to, to avoid or lower the amount of cleavage was determined.

Q. And does it give information as to whether glutamic acids will be cleaved under the various scenarios?

A. Yes.

Q. And how so?

A. Well, even in other solvents, there is some peptide cleavage. It's just that glacial acetic acid is the, shall we say, optimal solvent for cleavage or terrible solvent, if you want to avoid it.

Q. Now in our testimony, your earlier testimony, you indicated the effect of deprotection that occurred as a result of the HBr step disclosed in the '550 patent. Does this art that you've reviewed teach the person of ordinary skill in the art about

anything in addition to deprotection that would occur in that step using HBr?
A. Peptide cleavage, that there would be, as he says, extensive peptide bond cleavage, one might be able to lower it or eliminate by changing conditions of time and temperature.
Q. And would you expect that person of ordinary skill in the art performing the experiment to make a complex copolymer, in this case copolymer-1, to have gotten to this art in the natural course as a result of attempting to adjust the molecular weight ranges disclosed in that patent, the '550?
A. Yes, I would.
Q. Now, in addition to the references you've already noted, is there any other reference that you think the Court should see that that person of ordinary skill in the art would have had available to him?
A. Yes. If the person of ordinary skill would have continued minding the literature, he would've found another paper in a very reputable journal by Nylund and Miller, also referring to it Idleson and Blout, that also discusses peptide bond cleavage under these conditions.
Q. Nick, would you pull up please DTX-1784.
And, Doctor, what are we looking at here?
A. This is another article from the Journal of American Chemical Society published in 1965. It's States entitled synthesis and potentiometric titration of random copolymers of

L. lysine and L. glutamic acid.
Q. And the authors?
A. Robert Nylund and Wilmer Miller.
Q. Authors known to you?
A. No.
Q. Do you know where they were at that time?
A. The University of Iowa Department of Chemistry.
Q. Is this a reputable journal?
A. I mentioned that it's the premier journal in the field, yes.
Q. And is this a document that, or article that you relied on in forming the opinions that you have in this case?
A. Yes.
MR. SKILTON: Your Honor, I move into evidence DTX-1784.
MR. JAMES: No objection.
THE COURT: Admitted.
(Defendant's Exhibit 1784 received in evidence)
Q. What do Nylund and Miller say about the phenomenon of peptide bond cleavage by HBr?
And, Nick, would you turn to page 3541? And, Doctor, help us here to find it is?
A. Where it says, undoubtedly -- well, first of all, we can say the degree of polymerization, that is the size, was always lowered during the debenzylation.

Q. And what significance does that sentence have?
A. The next sentence after that; undoubtedly, peptide bond cleavage by HBr occurred, thus broadening the molecular weight distribution -- which is what I said, essentially, by breaking peptides into smaller fragments.
Q. All right. And again relate that statement or disclosure in that reference to the chemistry that you've been reviewing for the Court as disclosed in the '550 patent in 1971 Teitelbaum article?
A. Well, again, the degree of polymerization here refers to the size molecular weight, and the peptide bond cleavage would then lower this molecular weight, and to some extent broaden the molecular weight distribution by virtue of producing more lower molecular weight materials.
Q. Dr. Zeiger, from the perspective of a person of ordinary skill in the art, would that person have understood HBr cleavage to have occurred in the HBr treatment under the conditions described in the '550 patent?
A. Yes.
Q. Based on what you just described as the teachings of cleavage by HBr, would a person of ordinary skill understand that the '550 patent permits the production of copolymer-1 composition in the molecular weight of five to ten kilodaltons?
MR. JAMES: Objection, your Honor. I think that yesterday we have we had some discussion about difference

between size exclusion chromatography and other kinds of molecular weight measurements. I think that question is unclear as to what kind of molecular weight he's referring to.

MR. SKILTON: Your Honor, I could ask a question, if that's permissible.

THE COURT: Sure, go ahead.

Q. What kind of weight are you herein going to respond to my question using, what's your calculation?

A. Yes. Are we talking about molecular weights that I used in my publications and molecular weight profiles that I've published?

Q. Why don't we start with that as a foundation, and then I'll be more clear in terms of the reference point of the question. So with the Court's permission, would you add that information to the record?

THE COURT: Go ahead.

A. Yes. I've published the gel chromatography profiles of some of the sequential polypeptides that I have made, and I measure molecular weight by ultracentrifugation. I've never used size exclusion chromatography.

Q. All right. And when I asked you then --

A. For that purpose, I've used size exclusion chromatography but gel chromatography in terms of.

Q. Okay. So when I ask you the question in a range, explain to the Court what your understanding of the molecular weight is

of that range?
A. Well I've measured molecular weights by the two different ultracentrifugation methods, as well as by viscosity. And those are methods that are direct methods for measuring molecular weight, and those methods I'm -- I have been comfortable using in publishing.
Q. So when I am using this range, you're using measurements by either of those methods to as a reference point?
A. Mainly ultracentrifugation.
Q. Okay. With that as a qualifier, let me ask you the question again.

Based on what you just described as the teachings of cleavage by HBr, would a person of ordinary skill understand that the '550 patent permits the production of a copolymer-1 composition in the molecular weight of five to ten kilodaltons?
A. It is within the purview of a person of ordinary skill in the art to use time and temperature with this HBr and glacial acetic acid deprotection to obtain by manipulation a product in that range, yes.
Q. And what time and temperature variations would a person of ordinary skill in the art look to use?
A. Well, he would, he would vary them, and eventually come up with an optimal set of conditions for determining the molecular weight in the predetermined region that he wanted to go to.
Q. And I think we covered earlier, I'm not going to have you

do it again, but there are time and temperature variables disclosed in the 1971 Teitelbaum article, are there not?
A. There are references to -- that are given.
Q. That's the question I should have asked, be more specific. Are there references given to time and temperature?
A. The initial one is, is to Ben-Ishai and Berger, who used I believe 12 hours to overnight, and room temperature.
Q. Okay. Then would a person of ordinary skill in the art know that he or she could change the molecular weight ranges by optimizing the time and temperature variables in the process?
A. Yes.
Q. And why is that?
A. This is, as I mentioned, something that is taught in general chemistry, as well as peptide chemistry.
Q. Now, returning you, if you will, to the '550 patent text. Therein I think we'll find, if we look, that the copolymer therein reported was reported to be effective in the EAE model. First of all, do you understand what an EAE model is, Doctor?
A. I understand that it's a model from multiple sclerosis in laboratory animals.
Q. And have you worked with this model in your own work?
A. No I've not.
Q. Now, the model, did you have an understanding of it?
A. I believe I do, yes.
Q. And give the Court what the basis is of your understanding

of the EAE model is?
A. This is a situation in which demyelination of nerve sheath fibers occurs and, presumably, some sort of an immune consequence follows, which results in hind foot paralysis.
Q. And is this model that's used in animals?
A. The EAE model is used in animals.
Q. Now, would a person of ordinary skill in the art consider any additional steps in the process for preparing copolymer-1, prior to using the copolymer-1 in animal experiments?
A. Would you repeat that, please?
Q. Sure. Would a person of ordinary skill in the art consider any additional steps in the process for preparing copolymer-1 prior to using the copolymer-1 in animal experiments?
A. Yes, he would.
Q. And what step would he consider?
A. Some sort of purification or fractionation procedure to try to get rid of perhaps materials that are not peptide, for example.
Q. Is this purification, so to speak, a routine step?
A. Yes, it is. It's the bread and butter of a biochemist.
Q. And with respect to this particular purification, let me ask you about exhibit DTX-1783. What are we looking at here, Doctor?
A. This is the Katchulski and Sela paper that we cited -- we talked about earlier.

MR. SKILTON: And it is in evidence, I believe, your Honor.

Q. Let me turn here particularly to page 362, please, Nick. And highlight, if you would, the sentence beginning before, and through ensured. Thank you.

Doctor, would you read this sentence into the record, please?

A. Yes. In this review article on poly-amino acid synthesis, it says, before making use of the purified poly-amino acids in physicochemical or biological studies, the absence of low molecular weight impurities mentioned should be ensured.

Q. And what does this article in this sentence teach that person of ordinary skill in the art?

A. That one should try to purify or fractionate the polypeptide product before doing various physical chemical or biological studies.

Q. Now, I want to shift topics on you a little bit. I want to go to the question of ranges and first start the conversation by asking you a general question.

As of 1994, what would a person of ordinary skill in the art have expected about the distribution of sizes of the molecules in copolymer-1 batches prepared by the '550 patent process?

A. You would have expected an extremely polydisperse system.

Q. And when you say a poly dispersed system, give that a

little bit more content for the Court; what are you saying?
A. A wide range of size distributions of molecules in the product.
Q. And give us a little bit more of the, if you will, the physical chemistry of this; why is this -- what are we looking at, what are you describing?
A. Well, we're describing the results of a polymerization reaction. And the polymerization reaction itself certainly doesn't result in a single entity, and the degree to which it's not a single entity. Is a measure of the, or is a function of the dispersity. Polydisperse system just means that there is a tremendous variety in terms of the different sizes that are found.
Q. All right. And we've heard use of the word gamish by you, and descriptions of millions of billions and the like. Give the Court a little sense of copolymer-1 in terms of its polydispersity?
A. Well, I would expect from my own studies that one would expect a distribution over many kilodaltons in the product.
Q. All right. And I'll ask some more general questions, and then we'll get into some demonstratives. If one of ordinary skill in the art were to prepare two batches of copolymer-1 according to the '550 patent, what would that person have expected to see in terms of molecular weight distributions if the molecular weights were near each other?

A. One would have expected extensive overlap in these two batches in terms of the percent of size of molecules that are in common.

Q. And you'll have to define now another term for us, in the context of this mixture. What is overlap; what are you connoting?

A. Well, I think I just alluded to that. We're talking here about a percent of a given size of molecule in the two batches in common.

Q. Again, continuing at the more general plain that we're on, what would the person of ordinary skill have expected in 1994 concerning the chemical and biological properties of two batches of copolymer-1 that had substantial overlap in their molecular weight profiles?

MR. JAMES: Objection, your Honor. I think we're talking about size exclusion chromatography without saying the words size exclusion chromatography. He's talking about overlap and distributions, and I don't think he's laid any foundation for the fact that the techniques he was using and that he is testifying about today actually show a distribution from which you can determine whether there's overlap.

THE COURT: Do you want to explain that?

A. Yes. I did use size exclusion chromatography in my work and looked at molecular weights.

And in that respect whereas I did not use the size

exclusion for the purpose of utilizing standards, calibration standards, I certainly used other methodologies that were available.

Q. And as you approach these questions, as in the context of a person of ordinary skill in the art, do you believe you have that level of understanding of the various technologies involved in order to give the Court a helpful answer?

A. I believe so.

MR. SKILTON: Your Honor, I would approach this as a person of ordinary skill in the art and lay further foundation as requested by the Court.

MR. JAMES: Your Honor, if I may, could I ask a few questions of the witness on voir dire on the point of size exclusion chromatography experience?

THE COURT: I think it would be better left for cross, honestly.

MR. JAMES: Thank you.

THE COURT: I understand your point, but why don't we just wait and do cross.

MR. JAMES: Thank you, your Honor.

THE COURT: All right, go ahead.

MR. SKILTON: Thank you, your Honor.

Q. Let me repeat the question. By the way, did you teach gel filtration chromatography in your work at Jefferson?

A. Yes. I taught purification methods to medical students,

Ph.D. and master students.

Q. For how many years?

A. 35.

Q. All right, let's return to the question.

What would the person of ordinary skill have expected in 1994 concerning the chemical and biological properties of two batches of copolymer-1 that had substantial overlap in their molecular weight profiles?

MR. JAMES: Objection, your Honor. I don't think this witness has been qualified to give testimony on expectations with respect to biological properties.

MR. SKILTON: Your Honor, I think he was qualified in that word I stumbled over, immuno chemistry, and I'd be happy to pursue that right now if the Court requests.

THE COURT: I'm going to hear it, and I expect I'll hear more on cross, okay.

MR. JAMES: Thank you.

THE COURT: I just think it'll be easier, and probably more helpful to me. Thank you.

MR. JAMES: Thank you, your Honor.

THE COURT: Okay, go ahead.

MR. SKILTON: Should I read the question again, your Honor, or have it in mind?

THE COURT: Not unless Dr. Zeiger doesn't remember it.

THE WITNESS: I do remember it I believe, your Honor.

THE COURT: Okay, go ahead.

A. I have used immunogens extensively. In the course of my work, I mentioned that I immunized rabbits, guinea pigs, mice. And in particular, I have looked at such things as delayed hypersensitivity, immediate hypersensitivity, these are biological phenomena. Obviously I've not looked at every biological phenomenon in the, in the whole field, but nonetheless, nonetheless, I have some experience with study of biological properties and size.

(Continued on next page)

Q. I probably should have read the question, your Honor, so I will again. And what would the person of ordinary skill have expected in 1994 concerning the chemical and biological properties of two batches of copolymer-1 that had substantial overlap in their molecular weight profiles?
A. I would have expected him to perhaps anticipate that with an overwhelming or an extremely large percent of sizes in common, that there would be similar biological properties. This is clearly not a one-on-one absolute kind of level, but I would have expected him to anticipate this.
Q. Now, I'm going to switch you to the patents in suit, so keep the reference now, I guess new to what you've been answering. Do the patents in suit discuss this overlap you have been discussing concerning the molecular weight profiles of two copolymer-1 batches?
A. Yes, it does.
Q. And, Nick, please turn to PTX 1 already in evidence. And the Court has it all identified. So let's go to Figure 1 of the '808 patent, please, Nick.

In reference to what we've been talking about, Doctor, what is shown here?
A. Well, what's shown here is not the way that one would get the data from a size exclusion column, but one would, from a size exclusion column one would get some sort of detection of material, and the volume in which the material would come off

the column. What we see here is molecular weight profiles of three batches, according to the percent of total mass, which is calculated versus molecular weight as determined by some sort of calibration standard.

Q. And on the question of overlap that you've been discussing, is there anything shown that's of interest?

A. Well, the parties in common would be under the curves that you can see following the green line.

Q. And reading this graph, can you in light of the columns, or excuse me, the descriptions under molecular weight, what are the molecular weights, and we're using it as the Court, what are the peak molecular weights disclosed?

A. Well, there are two 7.7 batches and one 12.0 batch.

Q. All right, let's go, then, to Figure 2. First of all, more generally, what is the difference in what's being charted or graphed here between Figure 1 and Figure 2?

A. It's the same data from the same experiment, experiments, but the profile is plotted somewhat differently. Instead of percent of mass we're talking here about percent molar fraction. Percent mass kind of has a bias towards weight. The molar fraction kind of biases the numbers, the values towards the number of molecules in solution.

Q. All right, and we've heard a lot about molar fraction, but for purposes of this record, would you define molar fraction as you understand it?

A. Yes. If you take all the moles of the materials, moles meaning the number of molecules in solution and take a percent, you know, of them. In other words, the percent of the moles in the solution are then plotted against them like the weights.
Q. Again, relate this chart or graph to the question of overlap. What do we see here?
A. Again, following the green laser and you'll see that there is a considerable amount of overlap that's seen in this figure.
Q. Now, you've prepared a demonstrative to illustrate this?
A. Yes, I have.
Q. Nick, would you turn to the slide I think it's PTX 1, Figure 2 slide? Thank you. What is this, what are we looking at here?
A. So this is merely the overlap portion of the two profiles that were seen in the last Figure 2. You have the 7.7 batches and then the 12.0 kilodalton batch and the area in pink are those areas that have similar percentage of sizes based on molar fraction.
Q. And it would be a little more specific as to what's shown in the area of pink. What's the nature, if you will, of the mixture or the gamish that's illustrated by the pink color? What are you suggesting here?
A. So the moles of the sizes of the material are the same in terms of size under the two curves that are present in pink.
Q. Now, just looking at this disclosure from the '808 patent

Figure 2, when would a person of ordinary skill expect a batch of copolymer-1 having a molecular weight of 12 to have similar properties to a batch of 7.7?

A. Again, this is something that I would expect because the overwhelming number of molecules are in common. I would expect the molecules that are really there in common to kind of determine the overall, at least anticipate that they would determine the overall properties, biological properties in a solution.

Q. Again staying, if you will, with a constituency of what's illustrated in pink, what is the nature of the distributions; continuous?

A. Yes. The products of the polymerization as shown here are continuous products in terms of size distribution.

Q. And you said that you would expect within that pink area those products to have similar properties. Would you fill that out a little bit? What do you mean similar properties?

A. Well, it obviously depends what kind of properties we're talking about. But again, there are a lot of molecules that are in common. One would expect that the molecules in common would be the main determinant in terms of the biological properties.

Q. All right, now, have you in considering your evaluation of similar properties, similar constituency, looked at any other evidence in this case? In addition to Figure 2.

A. Yes, I have.
Q. And in particular, have you looked at what has already been admitted in evidence as the Alexander Gad report?
A. I have.
MR. SKILTON: Nick, would you pull up DTX 1704, please? Thank you. Your Honor, we provided here a redacted version that will be used. We have the original, of course, but for use in questioning.
THE COURT: All right.
Q. Let me point you to specific parts. Again to refresh the Court, this is a report by Alexander Gad from the analytical R&D department, and it is entitled, "Establishing an Analytical Link Between Early Clinical Trial Batches of Copolymer-1 and Current Production Batches." Do you have an understanding of who Dr. Gad was in reference to this time and this report, Doctor?
A. Only insofar as it says on the front page. I've never met Dr. Gad.
Q. Did you rely on this document or any information in it in forming any of the opinions in this case?
A. Yes, I did.
Q. Let's turn to page 4345, and particularly the introduction. Thank you. Let me see if I can get there fast. Nick, would you highlight the sentence in the first paragraph that begins "the indication claimed," and, Dr. Zeigler, would you state how

this information was used by you in coming to your analysis?
A. There were three batches that were obtained from the BR 1 clinical trials that I believe Dr. Bornstein conducted, and these batches were compared with a later batch that was synthesized by Teva.
Q. All right, and let me take you to another sentence here that begins "this report." Again, tell the Court how this information was important to you in forming your opinions.
A. Well, what Dr. Gad was interested in was comparing these earlier preparations from Weizmann and possibly Bio Yeda with a Teva batch later on in a variety of different ways, both chemical and immunological and biological.
Q. And Nick, take us to page 4346 under the methods section. Thank you. And at my request, will you highlight the first two sentences all the way through "standard"? All right, Doctor, what information was here used by you?
A. So there are three batches from the Weizmann Institute, and then number 320, 340 and 400, and these were compared with a Teva batch that was labeled 3494. The Weizmann batches were all prepared in the early '80s and the Teva batch in '94.
Q. All right, now, Nick, take us to 4349, please? And there are two diagrams here, Doctor. Did you rely on either one for your work in this case?
A. Yes. These are molecular weight profiles of the four batches that we just mentioned.

Q. Look to Figure B, please. Thank you, Nick. What is depicted in Figure B?
A. Again, these are the four molecular weight profiles of the batches under discussion.
Q. And is there any information on overlapping here compared from Figure B?
A. Yes, there's considerable overlap.
Q. Have you prepared slides here to demonstrate this concept of overlap that you've been discussing?
A. Yes, I have.
Q. Nick, would you go to slide 12 for us, please? All right, first on slide 12, Doctor, what information have you added to Figure B?
A. Yes. The three Weizmann batches, the 320 is 10.35 kilodaltons, the 340 batch was 13.45 kilodaltons and the 400 is 14.35 kilodaltons, and these are going to be compared to the Teva batch 03494 which was 7.15 kilodaltons.
Q. And anticipating a question or possibly a voir dire, what was your assumption of molecular weight measurement in kilodaltons in terms of how they were measured?
A. Well, they measured both in terms of size exclusion chromatography and ultracentrifugation. In this particular case, this was done by gel chromatography.
Q. Let's go to slide 13, please. And what information here have you highlighted in this next slide?

A. Yes, this is the degree of overlap by molar fraction in terms of the three Weizmann batches compared to the Teva batch.
Q. All right, now, in terms of the insert in the right hand upper corner which shows those numbers, Doctor, what's the source of that information?
A. Dr. Gad himself. This is a Teva calculated number.
Q. Is it taken from the report that we're looking at?
A. It is.
Q. And the title of this slide is, "Teva Calculated the Overlap of Polypeptides on a Molar Fraction Base as Between Teva and BR Batches." The answer you just gave explains that title, is that correct?
A. I hope so.
Q. So do I. Now, what is depicted here? What are you showing or what is being shown, better question, by that slide, on the question of overlap?
A. Specifically, that there is a tremendous amount of overlap in these three Weizmann batches to the Teva batch, ranging from about 75 percent to about 90 percent.
Q. And with your highlighter or the laser pointer, why don't we just show the Court the WIS 320 curve which has the 90 percent, 89.3 percent overlap.
A. That would be the one that is closest to the Teva batch.
Q. Okay, and again we established molecular weights for these curves?

A. That they were in the report.
Q. Let's go to the next slide. Slide 14, please.
A. Right.
Q. So what are we seeing here?
A. What we're seeing here are two of the curves here, the 7.15 kilodalton Teva batch compared to the 14.35 kilodalton Weizmann 400 batch. This is the one which if you take a look at the pink overlap area, you get close to 75 percent.
Q. And that's as, if you will, calculated by Dr. Gad himself, correct?
A. It is.
Q. And what would a person of ordinary skill understand from this amount or percent of overlap?
A. Well, the two curves differ in peak height by about twofold, about 7 kilodaltons, yet they're still 75 percent overlap. This really supports the whole idea of polydispersity of these products.
Q. How so?
A. Well, as I mentioned, again, the peak molecular weights are relatively far apart, that is, twofold, 7 kilodaltons apart, and yet one still has three quarters of the molecules that are in common.
Q. Okay. And then take us then to the next slide, 15, please? And the title of that is, "Over 80 Percent Overlap of Polypeptides on Molar Fraction Basis Between 7.15 and 13.45."

A. Yes. This is essentially --
Q. Would you for a moment narrate the slide?
A. I'm sorry. This is essentially the same treatment as we did in the slide earlier except instead of comparison to the 14.35, this is now comparison to the 13.45 batch, and you can see that we've gone by shifting one kilodalton over, so a 6 kilodalton difference and now we're up over 80 percent in common.

MR. SKILTON: Excuse me, your Honor.

Q. Would you turn to slide 16.
A. And this is just doing the same thing for the third set. This is the 10.35, the 7.15, and the two differ about three kilodaltons and yet the amount of overlap is approaching 90 percent.
Q. And what would a person of ordinary skill take from or understand from this amount of overlap?
A. Basically, that three kilodaltons isn't a whole heck of a lot in terms of distinguishing two different batches.
Q. All right, let's go back, if we could, Nick, to Exhibit 1704. And I refer you, please, to page 4356. And the sentence that begins, "The similar MW profiles," and that sentence through table 3.

Doctor, what's the significance of this sentence to you in forming your opinions in this case?
A. Well, the chromatographic profiles, namely, the, in

particular the molecular weight profiles of the three BR batches were compared to the Teva batch, and all four batches conform to the current specifications. The rest of the paragraph discusses some of the chemical and physical chemical comparisons of the batches.

Q. All right, and Nick, take us to page 4356, if you would, and the paragraph that reads "the most relevant." All right, Doctor, again, tell us how this paragraph, then, fits into your conclusions.

A. Yes, this is Dr. Gad's conclusion that the most relevant biological active tested, which is blocking of EAE in mice, again revealed that all batches are similarly active.

Q. It said highly active?

A. I'm sorry, highly active.

Q. Any other information you wish to point the Court to on this?

A. Yes, the fact that EAE is considered the best available model for multiple sclerosis, so this finding shows that batches used in the two well-controlled studies have similar structural, conformational characteristics that are relevant to their pharmacodynamic activity.

Q. And is this statement consistent with your opinions as a person of ordinary skill in the art in terms of what you would expect?

A. I think it supports what my expectations would have been.

Q. Now, Doctor, in your review -- we're done with this section, your Honor.

In your review of the prior art available to a person of ordinary skill in the art, did you have occasion to run into EP620, the 620 European patent application?

A. I have read it, yes.

Q. And Nick, would you please pull up DTX 1970? And, your Honor, this is not yet in evidence, so I'm going to do some formal --

THE COURT: Is there any objection?

MR. JAMES: We have no objection, your Honor.

MR. SKILTON: All right, your Honor, I'll go right to it then.

(Defendant's Exhibit DTX 1970 received in evidence)

Q. You have reviewed this document?

A. Yes, I have.

Q. And may I, for everybody's reference but particularly for yours refer to it as EP 620?

A. Yes.

Q. And did you rely on this document in coming to your opinions?

A. Yes, I did.

Q. Let's go to page 2 of DTX 1970 and beginning at line 50, please, Nick, and the paragraph that says "the synthesis," if you would, and highlight that. Doctor, what is being described

in this paragraph in Exhibit 1970?
A. Well, the idea here is to try to obtain a copolymer-1 like material, not via chemical synthesis, but via molecular biological means and methods.
Q. And does the last sentence of that paragraph explain what this experiment is all about?
A. Well, the patent hopes to improve upon the previous methodologies by incorporating each of the different polypeptides produced into a separate vector that can be isolated and immortalized.
Q. For the record, the sentence reads: "To generate a mixture of cop-1 polypeptides analogous to the chemically synthesized product, we produced cop-1 polypeptides from a pool of recombinant bacterial colonies containing cop-1 gene sequences, e.g. 1,000 colonies."

That's a mouthful. Could you convert this into why this was of interest to you, Dr. Zeigler?
A. Well, I was trying to follow clearly what was the intention of the patent, and the patent's intent was to be able to bring the disease of multiple sclerosis to a single or a few etiologies in terms of the polypeptides that are active.
Q. And, Nick, would you take us to page 3, please, of DTX 1970? And particularly, would you go to the paragraph I think beginning on line 8, which begins "the subject invention." And, Doctor, quickly, what is being disclosed that was

significant to you in this paragraph?
A. Again, the idea here of the molecular biology is that one would produce specific polynucleotides that would result in polypeptides that I guess hopefully should you like copolymer-1.
Q. And does it say, "Advantageously, the procedures of the subject invention can be used to produce polypeptides which may be useful in preventing, arresting or controlling demyelinating disorders such as multiple sclerosis"?
A. That's the goal of the patent.
Q. Incidentally, what is the date of this patent?
A. Could we have the original?
Q. If we could go back to the first page? The date of the application? I misspoke. Publication date appears to be 22.8.90. Do I read that correctly?
A. That's what it says, yes.
Q. As you read that, using the European system, what's the date?
A. August 22, 1990.
Q. Now go back, please, Nick, to that paragraph we were looking on on page 3? And, Doctor, read in the last sentence, that which begins, "more specifically"?
A. "More specifically, a preferred copolymer may consist of alanine, lysine, glutamic acid and tyrosine and have a molecular weight between about 5,000 and 50,000 daltons."

Q. Tell us how that sentence has relevance to you as a person of ordinary skill in the art in evaluating the work that you were asked to do in this case?
A. I would take away from this that the idea that Dr. Cook, from reading and knowing some of the previous studies with copolymer-1, thought that an active; biologically, medically active polypeptide could be anywhere between 5,000 and 50,000 daltons. There's no discrimination in terms of anywhere within this range.
Q. Now, Nick, please take us back to page 2, background of the invention. And here I would ask you to highlight the paragraph that begins at 11 and continues through 16. And, Doctor, the paragraph refers to work at the Weizmann Institute, refers to an article in the European Journal of Immunology, and an article in the New England Journal of Medicine. Would you fill out a little bit what is here being referred to, as well as, I might add, the '550 patent. What's being referred to?
A. Three of the works that we've discussed previously this morning. The European Journal of Immunology is the same as the Teitelbaum article. U.S. patent '550 we've gone through quite a bit, and the new England Journal of Medicine was a paper dealing with a clinical study by Dr. Murray Bornstein.
Q. What does that tell you as a person of ordinary skill in the art reading this particular patent application?
A. That the interest of the patentee is to not only duplicate

the advantages, the medical advantages of copolymer-1, but hopefully to first of all explain and understand the basis for it, and perhaps to result in perhaps complete removal of the exacerbation of the disease.

Q. Now, one of the articles you indicated was the Bornstein 1987 article?

A. Yes.

MR. SKILTON: And, Nick, would you turn to PTX 31, please? Your Honor, this is already in evidence.

THE COURT: Thank you.

Q. Doctor, first of all, this is an article that was published in what year?

A. In 1987.

Q. And we've been referring to it as the Bornstein 1987 article. Are you familiar with it by that term?

A. Yes, I am.

Q. You've reviewed this document?

A. I have.

Q. Did you rely on this document in formulating your opinion?

A. Yes, I did.

Q. And this is the document that is referred to in the '620 patent?

A. Yes.

Q. What does, from your point of view, what does Dr. Bornstein report at PTX 31?

A. Well, he used some, several different batches of copolymer-1 from the, from Israel, and these batches ranged in molecular weight from 14,000 to 23,000.
Q. And what does this, what information or, if you will, material considerations, what does this add to your opinion?
A. Certainly Dr. Bornstein felt that a 14,000 something molecular weight copolymer-1 batch was perfectly fine with regard to his clinical studies.
Q. Now, does the fact that the EP 620 patent application cites Bornstein's 1987 report of his clinical trial, the '550 patent and Teitelbaum 1971 suggest anything to you as a person of ordinary skill in the art performing the assignment that you were asked to perform?
A. Yes. That a variety of batch sizes are acceptable in terms of production of a copolymer-1.
Q. Now, I want to turn here to the '808 patent itself. And that would be, I believe, PTX 1. And here I want to point your specific attention to column 2, lines 14 through 27, and I'll read the sentence into the record that I want you to comment on. "Copolymer-1 according to the present invention may be prepared by methods known in the art, for example, the process disclosed in U.S. patent No. 3849550," and then it goes on to describe the chemistry.
Do you agree as a person of ordinary skill in the art that copolymer-1, according to the present invention, may be

prepared by methods known in the art?
A. Yes, I do.
Q. And what is the basis of that opinion?
A. Well, we've gone through the process step by step, and the steps appear conventional.
Q. Nick, would you slow slide 10, please? Now, what is the Court looking at here?
A. This is a comparison between the process as described in the '808 patent with the processes described in the '550 patent.
Q. And the left column of course as stated is the '808 and the right is the '550?
A. Yes.
Q. Taking you down to the word piperidine -- I'm not sure I pronounced that correctly -- in the '550 and to that 1 millimeter piperidine in the '808. Nick, could you highlight both portions? Down to that as ending points, how does the text of the two respectively compare to each other with reference to the procedures described?
A. They're extremely similar. The '808, of course, cites the '550 patent.
Q. And you said they're extremely similar. Are there differences in the recitations up to that point as between the two patents?
A. I just mentioned the '550. It's not word-for-word. For

all intents and purposes it's the same process.
Q. And what about temperature? How are the two comparisons, how are the two terms or patent descriptions comparable in reference to temperature?
A. Well, that the '808 patent process utilizes room temperature and discusses that as meaning 20 to 26 degrees centigrade.
Q. Now, does the '550 patent as read by you as a person of ordinary skill in the art describe the simultaneous cleavage step during the HBr in glacial acetic acid?
A. It does.
Q. Moving to the next paragraph, here, column 2, please, Nick, lines 28 through 45. Here, Doctor, I'll ask that the portion that is highlighted down to ultrafiltration be highlighted, and as a first step ask you to read the first sentence beginning at column 2, line 28 into the record.
A. "The copolymer-1 with the required molecular weight profile can be obtained either by methods known per se. Such methods include chromatography of copolymer-1 containing high molecular weight species and collecting the fractions without the undesired species or by partial acid or enzymatic hydrolysis to remove the high molecular weight species with subsequent purification by dialysis or ultrafiltration."
Q. First of all, do you agree with this, with these statements?

A. Well, I don't know whether I would call cleavage a purification, so I would have that -- that's a personal feeling, and I suppose that the patentees have got a right to define words the way that they wish.
Q. And as we get into the claims we're going to more specifically address your comment, but generally do you agree with respect to what you've read that these can be described as methods known per se.
A. Yes, I agree with the description of the second sentence by the end of the first sentence, methods known per se.
Q. Let me break it down a little bit more. First of all, what is chromatography?
A. Chromatography is the separation or fractionation of molecules.
Q. Do you have an example from the literature, for example, that was available circa May 23, 1994, to illustrate this method?
A. Yes. This method was applied certainly well before the '808 patent day.
Q. Nick, would you call out DTX 1806, please. Thank you. What are we looking at here, Doctor?
A. This is an article discussing the approach to the production of clinical grade dextrans.
Q. And the authors?
A. Barker, Ginetsos and Ajongren.

Q. The publication and date?
A. The publication is Journal of Chemical and Technologcal Biotechnology. The date is 1993
Q. And the accepted date is?
A. December 11, 1992.
Q. Is this publication a reputable publication?
A. I'm not familiar with it, but I have no reason to doubt it.
Q. Is this an article you relied on in forming your opinions in this case?
A. Yes, it is.
MR. SKILTON: Move into evidence DTX 1806?
MR. JAMES: No objection.
THE COURT: Admitted.
(Defendant's Exhibit DTX 1806 received in evidence)
Q. How does this Barker reference, if I may call it that, how does this Barker reference relate to the issue of polymerization?
A. Dextrans, of course, are polymers, but they're polysaccharides, and in that respect there are similarities and differences in terms of their synthesis. The dextrans can be polymerized again to very polydiverse mixtures to molecular weights even higher for that obtained for polypeptides and in particular dextrans have a role as blood volume expanders and are used in treatment of anemia. As a result it's very important for them to reach a clinical grade in which they can

be utilized in man.
Q. And Nick, would you go to page 21, please, and highlight the sentence that begins "before the".
All right, Doctor, what's being communicated by this sentence?
A. For this particular polymerization, it's discussing a desired range between 12 and 98 kilodaltons with an average that they would like to get of 40 kilodaltons.
Q. And go to page 25, please, Nick, part 5 of this same article, DTX 1806. And to the section that begins "fractionation of the native dextran product." What is herein being described, and relate it particularly to fractionation as you understand that term to be used in the '808 et seq patents?
A. The dextran products of polymerization can go into the millions. As I just mentioned, they want to get down to between 12 and 98,000, and consequently, they have to purify or fractionate the material. They use chromatography to fractionate, and they remove the high molecular weight stuff and incidentally acids treat the cleave into the 12 to 98 range so they don't lose all that material, and once they get rid of the high molecular weight, then they remove the lower molecular weight material fraction by filtration, ultrafiltration.
Q. So what's being described is what you understand to be and a person of ordinary skill would understand to be fractionation, is that correct?

A. Yes.
Q. For similar purposes?
A. Yes.
Q. And is this for purification to clinical standards of another polydispersed polymer?
A. It is, yes.
Q. Was this process as disclosed in this a process that was within the knowledge of a person of ordinary skill in the art circa May 24, 1994?
A. Yes.
Q. And were these methods that were known to you and taught to you, to students, graduate students at the Jefferson Medical College?
A. I have taught these methods, yes.
Q. All right, let's turn back to PTX 1, column 2, the patent in suit. And to that paragraph, Nick, if you would, that we were just highlighting. I want to go with the second method that was described in the same paragraph. All right. The second method now refers to partial acid hydrolysis. Do you see that?
A. I'm sorry.
Q. Maybe I've got the wrong sentence. So let's be sure to read it. It's the method that's mentioned in column 2. Are we at column 2? Are you following with me?
A. You're at the compositions?

Q. It says or by partial acids or enzymatic hydrolysis?
A. I do see that, yes.
Q. And what is this referring to?
A. Well, the partial acid hydrolysis I assume is discussing HBr in glacial acetic acid.
Q. To put a point on that, is peptide cleavage by HBr in glacial acetic acid an example of such a method?
A. I believe that's what they referring to, yes.
Q. And are there others?
A. I talked about enzymatic hydrolysis, which is a possible way of also treating the --
Q. Would you agree that partial acid hydrolysis is a method known per se in the art as of May of 1994?
A. Yes, I mentioned that earlier, yes.

MR. SKILTON: Your Honor, I'm at a point where I think I'm ready to go to the claims, and I project it's probably about 45 minutes. There are 23 claims involved.

THE COURT: All right. Why don't we take our afternoon break. I'll see everybody at 1:30.

(Luncheon recess)

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AFTERNOON SESSION

1:35 p.m.

THE COURT: All right, Mr. Skilton.

MR. SKILTON: Thank you, your Honor.

BY MR. SKILTON:

Q. Dr. Zeigler, we're going to now turn to the claims of the patents at suit and I will be asking your separate opinions as they relate to the claims separately.

Have you prepared some demonstratives to assist you and the Court following your testimony?

A. Yes, I have.

MR. SKILTON: Nick, I'd ask you to put the first demonstrative up on the board, that relating to the '808 patent.

Q. Doctor, let's first establish some parameters here. I will represent to you there are as I recall three slides that relate to the '808 and the asserted claim portion of that relates to the claim as written. I will be asking you in the first instance your opinion on obviousness as it relates to the claim as a whole, and then I'm going to be retracing a little bit to the elements of the claim so as to give the Court the benefit of your full opinion as it relates to each and every element of the claim.

So right now, Nick, would you scroll through, please, the three slides that relate to the '808 patent. Slide 2, then, separates out a purifying said copolymer-1 in the terms, your Honor, and the third slide, and would you go to the next slide with about 5 to 9, so please go back to slide one.

Doctor, looking at the language and the limitations

and terms of the claim as a whole, claim number 1 that we just reviewed, do you have an opinion as to whether that claim is obvious in your opinion to a person of ordinary skill in the art when considered on the date of May 24, 1994?

A. Yes, I do.

Q. And what is that opinion?

A. My opinion is that the entire claim is obvious.

Q. Now, we've looked at the portion of it, you see we've carved it out, and as to the portion that is on screen and ends with "aqueous piperidine solution to form copolymer-1," this chart also states, does it not a basis for that?

A. Yes. It does. This is, so far as I could see, completely covered by patent '550.

Q. And the red, then, need not be separately discussed. Your opinion, as I understand it, it says that all aspects of that are covered by the '550 disclosure, correct?

A. That is correct.

Q. Let's go to the second element that we've separated out for purposes of this discussion. "And purifying said copolymer-1." I think you earlier indicated that you saw two potential disclosures or methods of purifying in the '808 patent, and is that why you've broken this down into two sections?

A. Yes, it is. If you recall, we went through a sentence which ended "methods known per se," or also known per se or either known per se, I'm not quite sure, but following that,

there were two main examples, one dealing with chromatography, and one dealing with acid hydrolysis, and I'm assuming that this is what they were referring to when they used the word purifying.

Q. And with respect to the chromatography aspect or disclosure, do you have an opinion whether that adds anything new or novel to the claim as a whole?

A. No, it utilizes methodologies that were well known to people of ordinary skill in the art and the example that we discussed was Barker, et al, in terms of getting a clinical distribution of polypeptides with regard to dextran.

Q. And with respect to that second portion of the definition that at least as you read it, purifying equals acid hydrolysis HBr cleavage, in your opinion to a person of ordinary skill in the art was there any disclosure that added novel material or something within the claim as a whole?

A. No. Acid hydrolysis by HBr peptide cleavage as I mentioned was known for decades in the art.

Q. Would you go through the bases as stated, how do you reach that opinion based on the '550 patent?

A. The conditions of the '550 patent as followed by a trail through Ben-Ishai and Berger, Yaron and Berger, Edelstein and Blout, Yaron and Miller.

Q. That's essentially the basis that you have for that element. And then the third slide please, Nick. To result in

copolymer-1 having a molecular weight of about five to nine kilodaltons. Does that disclosure or element or limitation add anything novel to the claim as a whole?

A. Yes. I'm sorry. No. This is a claim that would have been obvious to somebody of ordinary skill in the art. For example, somebody that read some of my earlier papers which had been published by then, before then, that there is a great polydispersity in the products. To the extent that there would be a large amount of material in a product, copolymer-1 product, in excess of 10,000, which would be found in the 5 to 9 kilodalton range, and in support of this is the European patent 620 that disclosed copolymer-1 like compositions from their molecular biology techniques, technology, which was in a range that started as low as 5 kilodaltons.

Q. And you list as another basis, and I want to be specific in terms of what it says here, the overlap. Would you tell the Court how that basis relates to your opinion?

A. Well, it was not released to the public, so in that respect a person of ordinary skill would not have been exposed to that, but by the same token the results more than support the material that had been previously published that I referred to just above.

Q. All right, now, Nick, would you go to the slide that relates to the 589 patent, please? And here again we followed the same format?

A. Yes.
Q. Is it your opinion that the claim as a whole in all of its constituent elements or limitations would be obvious to a person of ordinary skill in the art?
A. Yes. This is a claim that still basically is covered by the patent '808 for the reasons state therein.
Q. All right, and when you say basis same as claim 1 of the '808, what are you trying to tell the Court with that entry?
A. Well, I'm not an expert in terms of the legality. I certainly don't want to make any -- you should pardon the expression -- claim towards that, but the counsel has mentioned that a claim, in this claim he cites a product made by a process as opposed to a product itself, the subtleties I'm afraid are beyond me, but nonetheless, this is what I've been taught to understand.
Q. All right, well, I will try to direct a question to you that notes the difference in the way the question is put rather than to ask you to understand the patent law distinction. But in any event, let me take the Court to what we're indicating, what you're indicating as saying for claim 1 of the '808 patent. Nick, would you take us back to the '808 slide? All right, and there you have stated and you go down the three charts bases for obviousness and is it your intent in stating it that way on the next slide to incorporate the bases that you recited for the '808 patent in explaining your opinion for the

589 patent?
A. Yes, I think that that will get us through the claims in a reasonable time period.
Q. All right. So let's pursue the note that is put there for your reference purposes. Claim recites a product made by a process. Focusing on the terms of the product described, is there anything novel about the product produced by that process in your opinion?
A. Not from our discussions previously, not from this process or product.
Q. And we can break that apart by first pointing your attention to the about 5 to 9 kilodaltons. Is there anything novel about that product?
A. No. Materials in that product would be present in a batch in excess of 10,000 kilodaltons.
Q. And made by a process comprising the steps of, again, that's as per what you explained in reference to the earlier patent, the '808 patent, is that correct?
A. That is correct, yes.
Q. And then may we go to the slide as it relates to the next set of claims asserted against Mylan and that is relating to the '847 patent. Nick, will you kindly go to that, please? There the claim recites the process, that's the second half of claim 1, and your basis for an opinion that the recitation in that element is the same as claim 1 of the '808?

A. Yes, it is. Just as it would contain 5 to 9 so it would contain about 4 to about 9 kilodaltons.
Q. All right, so let me ask you the overarching question. Is the claim as a whole and all its constituent elements in your opinion obvious to one of ordinary skill in the art as of the date?
A. Yes, Mr. Skilton, it would be.
Q. Here you see the element under copolymer-1 is not expressed in 5 to 9 terms but in 4 to 9 terms. Does that limitation or element add anything novel to the claim as a whole as it relates to this patent?
A. No, it would not.
Q. And why is that your opinion?
A. Because the process itself produces a polydispersed mixture and therefore would produce a product which certainly would contain a great deal of material below the in excess of 10,000, as I mentioned before.
Q. Okay. And so you relate back to the basis that you stated in the '808 opinion, correct?
A. That is correct.
Q. All right, let's go to the next claim asserted. It is also from the '847 patent. It reads: "Copolymer-1 made by the process of claim 1, wherein the process further comprises adding acetic acid subsequent to the treating step." Do you have an opinion as to whether that claim is obvious?

MR. JAMES: Objection, your Honor. This is not in Dr. Zeigler's expert reports.

MR. SKILTON: Your Honor, certainly the basis of it is and it's been covered in this record. May I rephrase it to indicate does he have a basis for an opinion?

THE COURT: I think you're asking the same question. I don't know whether I'll consider the testimony ultimately, but why don't you just get it out and then I'll take a look at your objection.

MR. SKILTON: All right, your Honor.

Q. Do you have an opinion as to whether or not that claim is obvious?

A. I do.

Q. And what is the basis for that?

A. The basis for that is reading the Goldberger and Anfinsen 1962 paper on one-molar piperidine in which they use acetic acid to change the pH and stop the reaction. That's a routine, trivial aspect of a biochemist.

Q. All right, let's go to the next patent in suit asserted against Mylan, and that is the '430 patent, please, nick. And first I believe there's only one slide relating to this, and so the claim as a whole appears on that slide. Do you have an opinion as to whether or not that claim as a whole would have been obvious to a person of ordinary skill in the art as of the operative date?

A. Yes, I have such an opinion.
Q. And what is that opinion?
A. My opinion is the polydiversity of the process producing such a copolymer-1 would indeed lead to over 75 percent of its molar fraction within the molecular range from about 2 kilodaltons to about 20 kilodaltons.
Q. What is the basis for your opinion that that element that you've recited, that that element is obvious?
A. Well, first of all, the kinds of experiments that have been published including by me dealing with polydispersity, and the degrees of overlap that are likely to result as a result of this dispersity, polydispersity.
Q. And you here list some additional bases for your obviousness opinion, first as it relates to the claim as a whole and with respect to this particular element. Would you take the Court through those bases as listed?
A. Yes. These offer support for the conclusion that I just gave that the Weizmann basis, 320, 340 and 400 all fall within this limitation, and in addition, one would expect the continuity, the contiguousness of these products to produce a composition of having similar properties.
Q. Similar properties as you earlier described in your testimony?
A. Yes.
Q. Now, this patent has additional claims asserted, if I'm

correct, so let's go to claims 2 and 3 of the '430 patent. These are also claims, your Honor, that are asserted by Teva against Mylan. And, Dr. Zeigler, let me focus your attention on claim 2. The copolymer-1 of claim 1, wherein said protected copolymer-1 is reacted with hydrobromic acid for about 10 to 50 hours at a temperature of about 20 to 28 degrees centigrade. Do you have an opinion as to whether that claim as a whole would have been obvious to and is obvious to one of ordinary skill in the art when analyzed on the operative date?

A. Yes. As I mentioned, somebody of ordinary skill that would come into my laboratory would be expected to know that one can vary and use temperature and time to control a chemical reaction.

Q. And here the note reminder to you and to me that this claim recites a product made by a process. Is the product therein recited novel in your opinion or would it have been so to a person of ordinary skill in the art?

A. In my opinion, yes, it would have been obvious.

Q. And let's go, then, to the next claim asserted against Mylan, 3. The copolymer-1 of claim 1, wherein said protected copolymer-1 is reacted with hydrobromic acid for about 17 hours at a temperature of about 26 degrees. Does that limitation, if you will, the new limitation added to that claim in any way change your opinion as to whether or not that claim as a whole as recited is obvious to one of ordinary skill in the art?

A. It doesn't change my opinion of obviousness. It just uses two specific parameters, 17 hours and 26 degrees, but it's still time and temperature.
Q. And why do those parameters or the manipulation of those parameters not add any novel limitation in your opinion as one of ordinary skill in the art?
A. Because someone would have been trained to understand that these parameters affect the reaction and in any case is shown explicitly in Yaron and Berger.
Q. So is it your opinion then that the claim as a whole as recited is obvious to one of ordinary skill in the art as of the operative date?
A. Yes, Mr. Skilton, it is.
Q. Let's go to the next set of claims asserted against Mylan. And here I refer to, Nick, patent '476. 6342476. Doctor, we have put that claim and its terms on the board for you to analyze for the Court. First of all, reading the claim as a whole and all of its limitations as recited therein, do you have an opinion as to whether or not that claim is or would have been obvious to a person of ordinary skill in the art circa May 24, 1994?
A. Yes. I have an opinion.
Q. What is that opinion?
A. My opinion is that the entire claim, meaning all of the individual limitations or parts of the claim, are obvious.

Q. And why don't you take the Court through some of the highlighted elements as shown in this slide and explain why none or any of these elements add novel material such as to take this claim out of obviousness.
A. Yes, let's start with treating multiple sclerosis. In terms of one of ordinary skill in the art who is not an expert per se in multiple sclerosis, he would have been told in the '550 patent that EAE is a model system for multiple sclerosis and on any account would have known from Bornstein in 1987 that copolymer-1 could be efficacious, could be used in terms of treating multiple sclerosis.
Q. The amount of copolymer-1 fraction wherein said fraction contains less than 5 percent, is that a novel limitation?
A. Of material of over 40 kilodaltons. Those two phrases I believe go together and this again would have been obvious, that is, especially as one went to lower molecular weights, that is, we talked about batches moving close together. If a batch moved towards in excess of ten, as it approached in excess of ten in my opinion less than 5% of the species of copolymer-1 would be over 40 kilodaltons and this again is supported by the internal Teva document by Dr. Gad.
Q. And that basis that you're alluding to is more fully stated, is it not, under the basis for obvious column on this slide?
A. Would you repeat that, please?

Q. Yes, the base that you're alluding to and described generally is more fully stated on the portion of the slide under basis for obviousness, correct?
A. Yes. I'm trying to streamline a little bit.
Q. I know you are. Thank you. And let's look at the over 75 percent of said copolymer-1 in said fraction is within a molecular weight range of about 2 kilodaltons to about 20 kilodaltons. Do you have an opinion as to whether or not this limitation adds new matter or is, would have been obvious to the person of ordinary skill in the art, and I'm going to rephrase the question to strike new matter so let me say it again, your Honor. It's a patent term I get confused on. Let me rephrase the question.

Does this limitation add any novel information or disclosure to the claim so as to render the claim non-obvious?
A. No, it doesn't. I talked a little bit about two kilodaltons to about 20 kilodaltons in a previous claim, and so far as I can see, the same reasoning would apply here as well.
Q. Because it's a wordy claim, state here the reasoning that you're employing for the Court's information. What is the reasoning that you are applying here to this set of limitations?
A. The size of the batch that's mentioned, at least within the molecular weight that Bornstein cites, plus the -- and the likelihood of this kind of a size distribution, as well as the

support that one can see by examining the Teva document by Dr. Gad.

Q. All right. Now, the last aspect or element of this claim says, "Wherein said copolymer-1 fraction is prepared by a process comprising the steps of," and there's a recital. What is your opinion as it relates to that element of the claim?

A. My opinion is that this has been previously disclosed as conventional.

Q. All right, let's turn, if we may, to patent '161. Doctor, you prepared a slide on '161?

A. Yes.

Q. And first looking at the claim as a whole as asserted, do you have an opinion as to whether or not that claim as a whole would have been and is obvious to one of ordinary skill in the art as circa the operative date?

A. In my opinion, it would be obvious as of May 1994 to a person of ordinary skill in the art.

Q. And here you list as a basis the same basis as claim 1 of the '476 and '430 patents. They are the patents we just reviewed?

A. Yes. From my scientific point of view, it seems that less than 5 percent over 40 kilodaltons and over 75 percent of about 2 kilodaltons to about 20 kilodaltons is obvious for the same reasons that I previously discussed.

Q. All right, and Nick, turn with us, please, to the slide on

U.S. patent number 7199098, the '098 patent. Doctor, here, would you state whether or not it is your opinion as to whether or not the claim as asserted, claim 1 in its entirety is and would have been obvious to a person of ordinary skill in the art circa the operative date?
A. To me, yes. It appears obvious. It contains the same elements that we had discussed in some of the earlier claims.
Q. And in addition you'll see an element that's been added, "The composition is suitable for treating multiple sclerosis." What is your opinion as to whether that element adds anything novel to the claim as a whole?
A. I believe that the article by Dr. Murray Bornstein covers the compositions of copolymer-1 that are suitable for treating multiple sclerosis, and I would rely on that as a person of ordinary skill.
Q. Now, claim 8 is a composition of claim 1, wherein less than 2.5 percent of the copolymers in the mixture have a molecular weight above 40 kilodaltons. What is your opinion as to whether or not that claim is obvious?
A. In my opinion, the claim is obvious for the same reasons given previously, that as one gets closer to an average molecular weight in excess of 10,000, one would indeed find less than 2-1/2 percent of the copolymers on a molecular weight range of about 40 KDA, kilodaltons.
Q. All right, now I'm going to turn to a little more

complicated claim, and that is the claims asserted under the patent number 6939539 by Teva as against Mylan. The claim 1 reads, "As a copolymer," etc. and you'll see there it has the feature of a molecular weight of about 4 to about 9 kilodaltons with the composition being suitable for treating multiple sclerosis. I'm paraphrasing.

Looking at the words as written in the context of the claim as a whole, do you have an opinion as to whether or not that claim is and would have been obvious to a person of ordinary skill in the art circa the operative date?

A. Yes, I do.

(Continue next page)

BY MR. SKILTON:

Q. And what is that opinion?

A. My opinion is that this would have been obvious to a person of ordinary skill in the art.

Q. Now, you'll note that the range limitations here are four to about nine kilodaltons. Tell the Court how that range enters into your analysis?

A. I discussed the polydispersity, and that the polydispersity doesn't stop at five. It would continue down to four, and even past four kilodaltons in terms of a batch that's polymerized by this technique. And, again, this conclusion is just reinforced by the data that Dr. Gad assembled.

As for the composition pock suitable for treating Multiple sclerosis, this is suggested in the '550 patent, and again more strongly supported by the Bornstein paper.

Q. All right. Now, looking at claim eight, I will state to you that that is stated as a dependent claim. You see that by its reference back to the composition of claim one, and wherein less than 2.5 percent of the polypeptides of the mixture on a molar fraction basis have a molecular weight of over 40 kilodaltons.

Is it -- do you have an opinion as to whether that claim, claim eight, the dependent claim, in combination with claim one, is or would have been obvious to a person of ordinary skill in the art circa the operative date?

A. Yes, I do. My opinion is that it would have been obvious.
Q. And explain that, please?
A. Well, we talked a little bit -- first of all, we talked about four to nine in discussing claim one. We discussed the composition suitable in claim one. And this adds less than two and a half percent the polypeptides molar fraction basis over 40 kilodaltons, and that is also a limitation claim that we have discussed previously.
Q. All right. And another dependent claim is nine asserted against us, and I will read that claim into the record.

The composition of claim eight, that which you just described, wherein over 75 percent of the polypeptides of the mixture on a molar fraction basis have a molecular weight in a range of about two kilodaltons to about 20 kilodaltons.

Do you have an opinion as to whether that claim, in combination with eight, and in combination with one, it would -- is and would have been obvious to a person of ordinary skill in the art circa the operative date?
A. I do.
Q. And what is that opinion?
A. My opinion is that it would have been obvious that all of the claim assertions in this patent would have been obvious to a person of ordinary skill in the art as of May 1994.
Q. All right, now let's go to the same patent claim ten. And here claim ten of the '539 patent reads: The composition of

claim nine, wherein the mixture has an average molecular weight of 6.25 to 8.4 kilodaltons.

First, with respect to that limitation on a stand alone basis, is there anything in your opinion that is not obvious about the molecular weight of 6.25 to 8.4 kilodaltons limitation?

A. None that I'm aware of, Mr. Skilton. In fact, it seems to me that that's encompassed by the claim of five to nine.

Q. And explain that briefly for the Court?

A. If I understand the claim correctly -- and obviously this is all a bit legalese and, therefore, perhaps not my major strength -- if I understand correctly, there's a previous claim of five to nine kilodaltons, and 6.25 to 8.4 would be encompassed within that claim, because the molecular diversity should be also approximately the same.

Q. All right. Now, with that as a predicate to the question, then I'll ask you whether the composition of claim nine -- and, Nick, would you slide back a slide? And remember you were asked about claim nine, which in turn refers to the claim eight, which in turn refers to claim one. And I ask you, going back to the slide that I'm looking at, is this series of claims, including the dependent claims, as expressed in the dependent claim ten, is that combination of claims obvious to one of ordinary skill in the art circa the operative date?

A. It would have been, yes.

Q. And you state your basis for that?
A. Yes, I have. Oh, again?
Q. Well, it's on the chart.
A. It's on the chart, and I believe we've covered that and I -- I don't want to burden the Court too much.
Q. Thank you. Okay. And then let's look at the last claim of '539 that's asserted. And it starts with a pharmaceutical composition, and we've highlighted aspects of the claim as written in red that we want you to focus your comments on; molecular weight of about four to nine to about nine kilodaltons, and a pharmaceutically acceptable excipient.

First, go through those one by one with a question in mind, do these elements of that claim add anything that would take the claim as a whole out of your opinion as to obviousness?
A. The phrase "a pharmaceutical composition," I don't remember if that's the exact phrase. But in claim one of the '550 patent, there is a use of the word pharmaceutical, which seems to indicate that all that is being done here is extending the copolymer-1 chemical mixture into a suitably deliverable pharmaceutical composition. I have no problem with that.

The molecular weight of about --
Q. When you say I have no problem with that, I'm not sure what you're telling the Court; what do you mean?
A. Oh. What I mean is that whereas I have not been involved

in the pharmaceutical industry, I have not been involved in dealing with the FDA, but I have been involved in preparing polypeptides. And it seems that the key to pharmaceutical composition is whether there is any kind of other elements that are in there that would affect the properties. I, from my understanding of '550, I don't see that.

Q. All right. Now let's go to the limitation molecular weight of about four to about nine. You covered that in your earlier testimony?

A. I did.

Q. And then the last one, a pharmaceutically acceptable excipient. Do you have an understanding of what that clause means?

A. I guess something that passes FDA inspection.

Q. All right. Now, does the '550 patent itself make any disclosures in the context of pharmaceutically acceptable?

A. I believe it does. May I read?

Q. Would you, please? It's stated, as you can see, as one of the bases that you listed as it relates to that claim. What are you referring to there?

A. Yes. I'm referring to claim one of '550, and I'm not going to read the entire claim one because the claim one itself is as long as some of these other claims. But if I may read the last phrase, from a semicolon? It says "In an amount effective for treatment or prevention of the said disease dispersed in a

pharmaceutically acceptable carrier for injectable administration."

So, firstly, I don't believe I have any difficulty with that, even though I have not worked with a pharmaceutical company, but in any case, it's been also disclosed in the claim in '550.

Q. So in sum, is it your opinion that claim 12 would have been obvious to one of ordinary skill in the art circa the operative date?

A. Yes. It is my opinion that this would have been obvious to a person of ordinary skill in the art.

Q. Now, I'm reminded that there are three more claims asserted against us from the '539 patent.

Would you show those claims? Thank you, Nick.

A. Well, 19 and 20 are not asserted, but are, nonetheless, there are claims that depend upon them.

Again, I'm not quite sure exactly from a legal position, but I can comment from a scientific position.

Q. All right, let me take you through it so the record is clear. I have a continuing slide relating to U.S. patent number 6,939,539 on the board, and I'm quoting -- we are quoting the asserted claim that we are now dealing with. There is of portion above, but let's go to 23.

23 is stated as a method for treating a patient suffering from multiple sclerosis comprising administering to a

patient in need thereof the pharmaceutical composition of claim 12.

Do you have an opinion as a person of ordinary skill in the art as to whether or not that claim is obvious?

A. Well, I think we'd have to go back to claim 12 again. I know that I have opined on claim 12, but I'm told that this is not a memory test, so.

Q. All right, there you are. And we've gone back in slides to came 12, and you see the claim is recited therein, and the opinion as stated?

A. I see it. Could we now go to 23?

Q. All right. And my question then I think better put, and thank you for helping me here, is is claim 23, in combination with the claim 12, is that combination, in your opinion, obvious to a person of ordinary skill in the art circa the operative date?

A. Yes, it is. Again, I would cite Bornstein as a basis for coming to this conclusion.

Q. All right. And 30 is -- states, a method for treating a patient suffering from Multiple sclerosis comprising administering to a patient in need thereof the pharmaceutical composition of claim 19.

So this takes us to claim 19, which I'll read in the record. 19, the pharmaceutical composition of claim 12, wherein less than 2.5 percent of the polypeptides of the

mixture, on a molar fraction basis have a molecular weight of over 40 kilodaltons.

And then, Nick, could you take us back to claim 12, so that he has the full context.

And claim 12 you just looked at, it's a long claim. You opined that it was obvious. And so that's your reference point, Doctor. Are you with me so far?

A. I am.

Q. All right, so let's go back, if we may, Nick, thank you, to the claim we're looking at. And that is 30, correct?

A. Yes.

Q. Do you have an opinion as to whether or not that claim, in combination with the other claims referenced is or is not obvious to a person of ordinary skill in the art circa the operative date?

A. I have such an opinion, and it is that this is an obvious claim.

Q. And on the basis -- you have same basis as claim one of the '476 and '430 patents. What are you therein referring to?

A. Some of the earlier patents that were issued that I have discussed.

Q. All right. And let's then go to claim 31. That claim, by its terms, depends on the combination of claim 20, so I'll read 20 into the record.

20, the pharmaceutical composition of claim 19,

wherein over 75 percent of the polypeptides of the mixture, on a molar fraction basis have a molecular weight in the range of about two kilodaltons to about 20 kilodaltons.

First, let me point your particular attention to those limitations in that claim. Have you already explained to the Court your basis as to why you think those limitations are obvious?

A. I believe that I have with regard to the each part of this claim.

Q. All right. And then take you to 31 again. No, I have to go back to 19, don't I. So let's go back to 19.

And have you likewise explained why each element in the claim as a whole of 19 would have been obvious to a person of ordinary skill in the art circa the operative date?

A. Yes. Again, I have opined on the others, and these are included in 31, and each of the parts to me appear to be obvious.

Q. All right. And so the question I have for you first, as we go down through this, do you have an opinion -- I don't think we can get on claim 23 -- thank you very much -- I think you've asserted it, your opinion is claim 23 in combination is obvious, is that correct?

A. That is, that is correct.

Q. For the reasons you explained?

A. Yes. And I just want to emphasize again that this is from

the position of a person of ordinary skill in the art, but it's my opinion.

Q. And 30?

A. The same.

Q. Do you have an opinion?

A. The same opinion, that this is obvious.

Q. And that is obvious with respect to the?

A. All the parts of the claim.

Q. All parts?

A. Up to there.

Q. Thank you. All parts of the claim as trailed through the dependent to the independent, is that correct?

A. That is correct.

Q. And then 31, do you have an opinion?

A. Yes. Again, going from 31, excuse me, back through this patent. All of the different aspects I believe are obvious and, therefore, asserted claim 31 is itself obvious.

Q. Dr. Zeiger, I'm pleased to report that we have now arrived to the last patent and set of claims asserted by Teva against Mylan.

So, Nick, would you please turn to U.S. patent number 6,048,898 and the chart related thereto.

Doctor, you see the words of claim one of that patent on the board?

A. I do.

Q. And you see there are certain limitations or elements of the claim that have been underscored in red in that demonstrative?
A. Yes, I see that.
Q. And would you take the Court through those in a very succinct way, please?
A. Yes. Here the individual, I guess the patentees are claiming to have a method of manufacturing copolymer-1 of a predetermined molecular weight profile, which is not stated, reacting the copolymer-1 with hydrobromic acid to form trifluoracetyl copolymer-1 having the predetermined molecular weight profile, wherein said reaction takes place for a time and at a temperature predetermined by test reaction.
Q. All right. And the Court has defined test reaction. And I don't want you -- I don't know if you need to see it, fine. But I'm asking you outside of the definition, and assuming the Court's definition, but to concentrate on the simple proposition of test reaction, and in particular predetermined test reactions. How, if at all, do these limitations or elements add to or contribute to your opinion as to whether or not this claim as written and as a whole is obvious to one or of ordinary skill in the art?
A. Mr. Skilton, I have an opinion at this point everywhere up to predetermined by test reaction. Because I would like to see, if I may, how the Court defines test reaction just to make

sure that there's no conflict in terms of my understanding.
Q. You've thrown a curve ball at me, Doctor. I tried to frame it so you didn't have to do it, but I think the question you put to me is fair, and probably the Court would want to see it too. So is there anyone --
THE COURT: I'm not going to answer it, that's for sure.
MR. SKILTON: Is there anyone who can help me in my time of need?
A. I'm sorry, but I'm a scientist and I want to make certain that it's not my opinion, but that it's the Court's opinion. Because ultimately the Court is the one that decides the issues here, and which is obvious to everybody here, but.
Q. We have the opinion. We're going to permit you to read it into the record or perhaps I will. If I don't read the right thing, I'm going to blame Ms. Glaser.
A. Yeah, I don't mean to take the Court's time, but I do mean to be as --
Q. All right.
A. -- specific as I can be.
MR. SKILTON: With the Court's permission, I'll read it?
THE COURT: You can give it to --
MR. SKILTON: I can give it to him, your Honor?
THE COURT: Dr. Zeiger, if you want.

MR. SKILTON: Thank you very much.

THE COURT: Sure.

Q. It's highlighted in green, the paragraph?

A. Thank you. Thank you, John, Mr. Skilton.

Q. Thank you. Okay, would you read what is highlighted, please, into the record?

A. Yes. For the reasons provided above, the Court construes predetermined by a test reaction to mean determined beforehand by a reaction carried out to determine results of varying reaction conditions.

Q. All right. Now then using that definition as the operative definition of the terms you see, do you have an opinion as to whether or not this claim as a whole as written, with all limitations would have been obvious to a person of ordinary skill in the art circa the operative date?

A. I do have such an opinion.

Q. And what is that opinion, Dr. Zeiger?

A. The opinion is that this claim, as well as all the others -- I'm sorry, it's only one claim -- this opinion, this claim is obvious.

Q. And what about this phrase or concept of predetermined in testing, how does that fit into your opinion that the claim is obvious?

A. The definition, as the Court defined it, is very clear, and I believe does not change my opinion with regard to the entire

claim.
Q. And can you explain what you mean by that last statement; why does it not change your opinion?
A. Because, presumably, by changing time and temperature, one can reach a lower molecular weight of any size and range -- well, I shouldn't say any size and range, but certainly molecular weight average that one predetermines that one wants.
Q. And once you predetermine it, how, if at all, does the testing step relate to that?
A. One can utilize this testing step as a teaching tool in order to achieve it in future experiments.
Q. All right. And is it your opinion that those elements or limitations of the claim add nothing now or to the claim as a whole?
A. Yes, that's correct.
Q. To one of ordinary skill in the art, circa the operative date, is that correct?
A. Yes, that's the conditions, the situation as which I am opining under.
Q. And are the other bases for that obviousness opinion summarized in the basis for obviousness on this chart?
A. Yes. We have the Bornstein paper, the '550 patent and, of course very importantly, the Yaron Berger paper, which state in a certain aspect the obvious use of time and temperature to affect reaction results.

Q. Okay. Now, there are claims two and three of this patent that are also asserted. Let's look separately at claim two, which I'll read into the record.

The method of claim one, wherein said protected copolymer reacted with hydrobromic acid for about ten to 50 hours at a temperature of about 20 to 28 degrees centigrade.

Do you find that element, in combination with the asserted claim one, which you've just been through, to be obvious to a person of ordinary skill in the art circa the operative date?

A. I would, Mr. Skilton, and I would fine it to be obvious.

Q. And, again, the basis is stated as the same as 898. Can you fill it out a little bit? These are specific experimental conditions that are recited. How, why do you find those to be obvious?

A. Because time and temperature, excuse me, are the variables by which one can manipulate the degree of cleavage by the HBr and glacial acetic acid reaction.

Q. All right. And then take you to claim three?

A. Pretty much the same thing. These are specific, a specific time, a specific temperature, which are covered within the ranges that are mentioned in claim two. So I don't see anything more usual or different than merely utilizing one specific time and one specific temperature.

Q. All right, sir, do you have an opinion as to whether the

dependent claim two, which reads through claim, excuse me, the dependent claim three, which reads through claim two, and includes claim one, that combination in whole, as a whole would have been obvious to a person of ordinary skill in the art circa the operative date?

A. Yes, I have such an opinion, and my opinion is that this claim three, as you just cited, would have been obvious to a person of ordinary skill in the art as of May, 1994.

MR. SKILTON: Thank you, your Honor.

Thank you, Dr. Zeiger. That concludes the direct examination.

THE COURT: All right. Thanks, Mr. Skilton. Cross-examination.

CROSS EXAMINATION

BY MR. JAMES:

Q. Good afternoon, Dr. Zeiger.

A. Hello, Mr. James, how are you?

Q. I'm very well.

MR. JAMES: Based on that exchange, your Honor will understand we met before when I took Dr. Zeiger's deposition?

THE COURT: All right.

Q. Now, Dr. Zeiger, you never measured the molecular weight of a copolymer using size exclusion chromatography, have you?

A. Would you just repeat that one more time?

Q. You have never measured the molecular weight of a copolymer

using size exclusion chromatography?
A. That is correct.
Q. And you don't recall having ever generated a molecular weight distribution curve, correct?
A. That was correct at the time of the deposition, that I didn't recall it. But in fact I have since had the opportunity to redo or at least, I'm sorry, to look at my earlier papers, and I do have a size exclusion chromatography. That is a gel chromatography in which the materials or at least fractionated materials were examined for molecular weight. So, I'm sorry, but at that time my memory was a little faulty.
Q. And you've never designed any calibration standards for size exclusion chromatography, have you?
A. That is correct.
Q. You never have done research into the fundamental underpinnings of size exclusion chromatography, right?
A. That is correct.
Q. And none of your publications disclose a -- I'll strike that, come back.

I believe you said earlier today, Dr. Zeiger, that you don't hold yourself out as an expert in size exclusion chromatography, correct?
A. Insofar as the use of calibrants is concerned, that's correct. But I have used size exclusion chromatography going back to my post doc days with Chris Anfinsen.

Q. All right. Now Dr. Zeiger, let's put up slide -- you testified extensively about the '550 patent today, correct?
A. Yes, I did.
Q. And you testified on your direct examination that the '550 patent discloses a copolymer-1 one with the molecular weight of 10,000 daltons correct?
A. To be exact, in excess of 10,000 daltons. I believe that's the language.
Q. And in support of that testimony, you pointed to column one of the '550 patent, right?
A. What word? I'm sorry, I missed a word that you said.
Q. In support of your testimony, you pointed the Court to column one of the '550 patent?
A. Yes.
Q. If we could pull that up, Mr. Chase. And in particular, Mr. Chase -- yes, if you could pull up the paragraph beginning at about lines 57 in column one of the '550 patent. And could you highlight the sentence -- let's just highlight the entirety of the paragraph from the novel compositions down to electrical charge, Mr. Chase.
Dr. Zeiger, the portion of column one of the '550 patent that I have highlighted, that's the portion of the '550 patent that you pointed the Court to today in your testimony, that copolymer-1 -- there's a copolymer-1 in excess of 10,000 disclosed in the '550 patent, correct?

A. That's one of I believe five numbers that are used somewhere in the '550 patent. But that is correct, we did talk about that, yes.
Q. But, in fact, that is not a specific description of copolymer-1, is it?
A. I'm not sure what a specific composition of copolymer-1 is. I don't believe any one molecular weight was, you know, was specified. So if you can help me out there a little bit in terms of the definition, I could answer that.
Q. Well, that paragraph does not specifically describe copolymer-1, correct, Dr. Zeiger?
A. It doesn't use the word co-polymer-1, but that is certainly one of the, if not the main product that the, that the patent refers to. But if you're asking does it actually use the word copolymer-1, it does not.
Q. I'm not asking you if it uses the words copolymer-1. I'm asking you, Dr. Zeiger, whether it's a specific description of copolymer-1?
A. It's not specific because it includes other, other potential materials with positive electric charge and other materials possibly with negative electrical charge.

So you're right, in that respect if that's what you're referring to, it is not specific to copolymer-1.
Q. It doesn't list the amino acids that are found in co-polymer-1 in that paragraph, correct?

A. That's essentially what I was saying in terms of net positive electric charge, both that is net positive and negative electrical charge, I think, I think that's what I addressed, yes.
Q. So the answer to my question is that it does not specifically identify the amino acids found in copolymer-1, correct?
A. I was being wordy. You're right.
Q. And it doesn't describe the molar ratio of the amino acids that are found in copolymer-1 in that paragraph, does it, Dr. Zeiger?
A. That is correct.
Q. Now let's look at column two of the '550 patent, another -- and in particular, I'm sorry, lines 19 to 26. And this was a section of the patent specification you also directed the Court's attention to. And in this section it discusses a preferred copolymer, correct?
A. Yes.
Q. And this copolymer is made of alanine, glutamic acid, lysine and tyrosine; isn't that right?
A. Yes, it is.
Q. And at the bottom it says that they are found in a molar ratio of 6 to 2 to 4.5 to 1, correct?
A. Yes, it does say that, yes.
Q. And that's copolymer-1, correct?

A. Yes.
Q. So that paragraph is a specific description of copolymer-1 isn't that right, Dr. Zeiger?
A. I'm not quite certain, because the sentence right after starts with similar results were obtained, and, therefore, I wouldn't know exactly whether to stop it there or to continue in terms of the definition. My --
Q. We can look at that sentence. It says, similar results were obtained with a soluble copolymer comprising tyrosine, aspartic acid, alanine and lysine. You see that?
A. I do.
Q. That's not copolymer-1, is it?
A. That's correct.
Q. So the specific portion of this patent that describes copolymer-1 is a portion that I just went through with you from lines 19 to 26 of column two, correct?
A. Yes, but it doesn't -- again, it doesn't use the word copolymer-1 and, therefore, I could well have read the, the last sentence as being included in the beginning parts of the paragraph.
Q. But with respect to the molecular weight for the portion that we've agreed is copolymer-1, the molecular weight stated there is 20,000, 25,000, right?
A. Yes. But what I'm saying is that could also include tyrosine, aspartic acid, alanine and lysine, and glutamic acid

lysine -- I'm sorry, alanine and lysine.

What you're saying is correct, but I'm stating that I could understand that sentence to be more than a specific reference to copolymer-1.

Q. You also directed the Court's attention to the claim of the '550 patent, right?

A. Yes, I did.

Q. Let's pull that up, please, Mr. Chase. And the claim discloses in part one in the middle, alanine, glutamic acid, lysine and tyrosine in the molar ratio of about six parts alanine to two parts glutamic acid to 4.5 parts lysine to one part tyrosine; you see that?

A. I do.

Q. That is a specific description of copolymer-1, correct?

A. Yes, that is.

Q. And the molecular weights stated there in claim one is 15,000 to 25,000, right?

A. Yes, it does.

Q. And that would suggest to a person of skill in the art that the molecular weight of copolymer-1 disclosed in the '550 patent is in the range of 15 to 25,000 daltons, right?

A. Well, for the reasons I mentioned earlier, I think somebody reading the patent would have seen all of the numbers.

But in terms of the claim what you're saying is correct, but in terms of the entirety of the patent, one, I

believe, would have to look at the entire range that's disclosed.

Q. Well, the only specific disclosures of copolymer-1 that you and I looked at so far list molecular weights from 15 to 25,000, correct?

A. Well, that's what this particular claim says.

Q. And that's what the portion of column two we looked at said, right?

A. Well, that's said 20 to 25,000, which is a different range.

Q. It would be embraced within 15 to 25, correct?

A. Of course.

Q. Now, Dr. Zeiger, you're aware that Mylan submitted an application to sell a generic version of copolymer-1, to the FDA, correct?

A. I am aware of that.

Q. And have you reviewed that submission, or any part of it?

A. Is it in my expert reports?

Q. Did you ask to review it to see how Mylan characterized the '550 patent before you offered your opinions in this case, Dr. Zeiger?

A. I don't -- this -- I've been involved in the case, as you well know from my expert reports, for almost a year. So my memory specific with regard to some of the specifics may be a little bit faulty.

I have looked at some documents from Mylan and from

Natco. But in terms of what you're referring to, I don't have any recollection that I have.

MR. JAMES: Your Honor, with your permission, I'll hand an exhibit to the witness and hand it up to the Court.

THE COURT: Sure. Just identify it.

THE WITNESS: Thank you.

MR. SKILTON: Mr. James -- your Honor, may I have a minute to consult on this document?

THE COURT: Sure.

MR. SKILTON: Your Honor, may I consult with Mr. James?

THE COURT: Yes.

MR. SKILTON: Thank you, your Honor.

MR. JAMES: For the record, PTX-327 is a Mylan production document. It is a -- it's an excerpt from a document that's already in evidence, which was PTX-320.

THE COURT: Okay.

Q. And Dr. Zeiger, I just want to direct your attention to one page of the document, which is MYL16.

A. Yes, I have that.

Q. And the third paragraph of that on that page it says, "Overview of the process." Do you see that?

A. I see that as the headline of that page.

Q. Right. And then in the third paragraph there's a discussion of the '550 patent, correct?

A. Yes.
Q. And it says in the last sentence, describing the -- well, let's just read it together, maybe that's better. It says, "Later U.S. patent 3,849,550, 1974, application dated 1971 by Sela, Arnon and co-workers describes the preparation of glatiramer acetate under the title therapeutic copolymer."
You see that?
A. I do.
Q. It says, "The procedure described here is the same as what was described in European Journal of Immunology, 1971, 242 to 248." You see that?
A. I do, yes.
Q. And that's saying that the, just as you testified earlier today, that it's the same process in the European Journal of Immunology as is disclosed in the '550 patent, correct?
A. Yes, that is correct.
Q. And the last sentence says, "The molecular weight of the copolymer achieved was greater than 15,000 and less than 25,000 daltons." You see that?
A. I do.
Q. You agree with that, right, Dr. Zeiger?
A. I agree that that's the sentence there, yes.
Q. You agree that the '550 patent describes copolymer-1 having molecular weight between 15 and 25,000 daltons, correct?
A. That was in the claim. I'm not in a position legally to

decide the specifics of what the boundaries of copolymer-1 are. I'm in a position of saying that I, as a person of ordinary skill in the art, particularly somebody that has had experience or at least some knowledge of polymerization synthesis, would conclude.

Q. You have no reason to disagree with Mylan's characterization of the '550 patent to the United States Food and Drug Administration, do you, Dr. Zeiger?

MR. SKILTON: Your Honor, I object, mischaracterizes.

THE COURT: I think he's answered the question.

Q. Now, Dr. Zeiger, going back to the '550 patent. You would agree that there is no express reference to a copolymer-1 having an average molecular weight between five and nine kilodaltons, correct?

A. Yes, that is correct.

Q. And you would agree that in the '550 patent, there is no express reference to a copolymer-1 having an average molecular weight between about four and about nine kilodaltons, right?

A. Yes, that is correct.

Q. And you would agree that there is no express reference in the '550 patent to a copolymer-1 having an average molecular weight between 6.25 and 8.4 kilodaltons?

A. Yes, that's correct.

Q. And, in fact, Dr. Zeiger, the '550 patent doesn't disclose any measure molecular weight values for any batch of

copolymer-1, does it?
A. All it does is refer to the Teitelbaum paper, in which there are molecular weight that are discussed. And, interestingly, that molecular weight is not among the numbers that are given in '550.
Q. I think the answer was yes, but I'll ask it again. There are no measured molecular weight values for any batch of copolymer-1 in the '550 patent itself, correct?
A. Yeah, I'm not trying to avoid the answer to the question. I'm trying to give the answer as best as I can.

I believe that disclosure, if I'm correct, also includes references that are in the patent and, therefore, if it includes the references, I would also add the 23,000 molecular weight that is obtained in the European Journal of Immunology. But if I'm wrong, I'm sure you'll tell me so.
Q. So just to make sure we're clear, in the '550 patent itself within the four corners of that document, there is no measured molecular weight for a copolymer-1 batch?
A. You're right, Mr. James.
Q. But in, you're saying that in the Teitelbaum reference there are some measured molecular weight values, correct?
A. Yes.
Q. Let's look at slide 19 from Dr. Zeiger's presentation. And, Dr. Zeiger, it's your opinion and stated on this slide, that claim one of the '808 patent is obvious over the '550

patent, correct?
A. Yes, that is correct.
Q. And in particular, it's your opinion that an average molecular weight of about five to nine kilodaltons was obvious over the '550 patent, right?
A. Yes, that is correct.
Q. And you understand that the Court has construed the term average molecular weight in this case, correct?
A. Yes.
Q. And you've reviewed the Court's claim construction?
A. I have. But if you could remind me, if I can see it again. I don't believe this is a memory examination.
Q. I believe I can do that.
A. Thank you.
Q. I've put on the screen the Court's construction of average molecular weight is a peak molecular weight detected using an appropriately calibrated suitable gel filtration column. You see that?
A. Yes, and I remember that.
Q. And you understand that peak molecular weight is the molecular weight that is read from the peak of a chromatogram, correct?
A. Yes, that is correct.
Q. Now, it's your opinion that the disclosure in the '550 patent overlaps or is adjacent to the profile of about five to

nine kilodaltons, right?
A. Well, that's what I say over here. But, in fact, I believe it goes to four to nine and even beyond that, and that's one direction.
There's also -- well, in terms of overlap, that's correct. The answer to your question is yes, but its more than that, at least.
Q. But you're not suggesting that the overlap that you're talking about in that bullet on the right-hand slide, right-hand side of slide 19, that that is a peak molecular weight between five and nine kilodaltons, are you?
A. You're right, that is correct.
Q. And, in fact, there is no overlap in peak molecular weights between the claims, the asserted claims in the patents in suit and the '550 patent, is there?
A. That is correct.
Q. Now, at the bottom of slide 19, you say "Because of the substantial overlap in the molecular weight distributions of copolymer-1 composition is known in the art." You see that?
A. I do.
Q. And then you list three batches that are followed by the -- I mean that follow the prefix WIS; you see that?
A. Yes, I do.
Q. And those are batches that were used in the original Bornstein clinical trial, correct?

A. Yes, I believe so. I've seen the numbers, and I'm quite certain that those are included in them.
Q. Those batches were not available to the public, correct?
A. That is correct.
Q. In fact, they were part of a clinical trial in which they were experimenting on the use of copolymer-1 to treat multiple sclerosis, right?
A. That is correct, yes.
Q. Those batches that you list on this slide, they were not available to a person of skill in the art in 1994, correct?
A. That is correct. I wrote this as a scientist, rather than as a patent attorney. You're absolutely right.
Q. And at the bottom of that bullet, you say "A person of skill in the art would expect such compositions to have similar properties." Do you see that?
A. Yes.
Q. But those batches were not in the prior art so that a person of skill in the art could form an expectation on their basis, right?
A. Well, you're talking about those particular batches. And, again, my experience and knowledge of the literature includes the sorts of polymerizations and polymers and products that we're talking about, but not copolymer-1.
Q. Right. Those copolymer-1 batches that you list on the right-hand side of slide 19, those batches were not in the

prior art, and they couldn't form the basis for an expectation for a person of skill in the art, could they?

A. It's not that -- you're right, that I would depend on. It is more my -- not only experience, but also my reading of the literature.

But you're right, I miswrote, I believe, if I understand legally, I think you're quite right, that these would not have been considered as prior art, because they were not available to the public.

Q. And the second part of your basis, your support for your opinion in that parenthetical on the lower right-hand side is figure two of the patents in suit, right?

A. Would you say that again, please?

Q. Yes. In the lower right-hand side you say, you have your statement about how the overlap in the molecular weight distributions would give rise to an expectation of similar properties. And in the parenthetical you list two different bases for that, right? One is the batches of copolymer-1 used in the Bornstein trial we already discussed, right?

A. Yes.

Q. And the second basis is figure two of the patents in suit, correct?

A. Yes, that's correct.

Q. And figure two of the patents in suit, that wasn't in the prior art either, was it?

A. No, it was not.
Q. But figure two was available to the patent examiner when he examined these claims, correct?
A. Yes.
Q. And figure two was available for him to compare it to the '550 patent, correct?
A. It was.
Q. And the patent examiner allowed these claims over the '550 patent in view of figure two, correct?
A. Yes, that is correct.
Q. Let's look for a moment at the 1987 Bornstein paper -- I'm sorry, that's the wrong exhibit, Mr. Chase. I believe it's DTX-1228 in your binder, Dr. Zeiger?
A. Do I have it in my binder?
Q. I believe you do. I'm going to put it on the screen, but feel free to look at it in your binder as well.
A. Oh, yes. I know. I didn't have those numbers memorized, I'm afraid.
Q. 1987 Bornstein paper, that was something you disclosed or discussed in your direct examination, right?
A. Yes.
Q. And it discloses co-polymer-1 having molecular weights between 14,000 and 23,000 daltons, right?
A. It does.
Q. But there's no molecular weight distribution curve provided

for those batches, is there?
A. No, there is not.
Q. There are no peak molecular weights for those batches, correct?
A. Specifically no peak molecular weight batches.
Q. The specific molecular weights of the batches that were used in the 1987 Bornstein trial, they were not known to the public in 1994, correct?
A. I believe that that's correct. I have not seen -- you know, I've not looked for publication in perhaps the Arnon Sela documents. That is their publications. I would assume that you're correct.
Q. If we can go back to slide 19, Mr. Chase.

Now, Dr. Zeiger, I want to make sure I understand your position on the obviousness of the claims. Your position is that the person of skill in the art in 1994 would have looked at the '550 patent and its description of copolymer-1, correct?
A. That's certainly one of the places that would be foremost in a POSITA trail, so to speak, of the '808 patent in suit, yes.
Q. And the second part of the trail would be that you would look at the -- if we could look, Mr. Chase at the -- if we could look at the '550 patent just for a moment. I believe it's PTX-26. And if we look at the last page.

So the trail begins at the '550 patent, right, Dr.

Zeiger?
A. In my opinion, yes.
Q. And then you look at the '550 patent to the last page and you see a reference to Teitelbaum 1971 under other references, correct?
A. Yes.
Q. And it's your position then that you look at the Teitelbaum 1971 paper, that's PTX-499, you look at the Teitelbaum 1971 paper, Dr. Zeiger, and you see a description of how to make copolymer-1, correct?
A. Yes.
Q. If we could pull up the left-hand side of page 243, please, Mr. Chase.

And in this section, Dr. Zeiger, you pointed the Court to the fact that the deblocking of the, is that a gamma?
A. Yes, it is.
Q. The deblocking of the gamma carboxyl groups of the glutamic acid was carried out with hydrogen bromine in glacial acetic acid, and then you go to footnote 16, correct?
A. Yes.
Q. And if we could pull up footnote 16. Footnote 16 is a reference to the Ben-Ishai article, correct?
A. Yes.
Q. And so we -- the next little part of the trail is that we, now we go to 1759?

A. Is that reference 17?
Q. That's reference 16.
A. Oh, I'm sorry.
Q. We can show it on the screen, but, or you can look in your binder there. But I'll represent to you that footnote 16 was the Ben-Ishai article, and we have that up, it's DTX-1759.
And DTX-1759, that's not about a peptide, correct?
A. You're right.
Q. But it is about the use of HBr and acetic acid?
A. Yes, to deprotect benzyl-esters.
Q. To deprotect benzyl-esters of?
A. Of amino acid, on amino acid.
Q. De-puric acid?
A. Yes, specifically.
Q. Right? And there was no cleavage of any peptide bond there, right?
A. Yes, that is correct.
Q. Because if there would have been clean of the peptide bond, you wouldn't have had de-puric acid, right?
A. Yes.
Q. So the person of skill looks at the 1971 Teitelbaum paper, finds the reference to Ben-Ishai, sees that the second author is a person named Arieh Berger, and then I think you testified that what they do next is they go and investigate all of the papers written by Arieh Berger, right?

A. That's what I would do if I were trying to follow a literature trail.
Q. And what they would do if they read all the Berger papers, is they would find the Arnon Berger article that you referenced, that's DTX-1994?
A. In that particular case, they could have walked down the hall and done that.
Q. In 1994?
A. I'm sorry. You're talking about a person of ordinary skill. I was talking about the patentees.
Q. Right. The person of ordinary skill in 1994.
So far, I have your explanation of how you get to your obviousness --
A. Yes.
Q. -- argument, right?
A. Yes, that's correct.
Q. So you find this paper DTX-1934, and it relates to poly-amino acids by Yaron and Berger, correct?
A. Yes.
Q. And in that paper there is no cleavage reported of those polymer chains, correct?
A. There is no cleavage reported. There's an acknowledgement that cleavage would be expected.
Q. There was an acknowledgement -- there was a citation, actually, to --

A. Yes.
Q. -- another paper, right?
A. Right, with the followup saying that because of this paper here, we were concerned about -- I forgot the exact words. If you can take me to it, I can read it, or otherwise we can just accept the testimony that I gave earlier, whatever you prefer.
Q. Well, I think what you said was that you would look at Yaron and Berger article and then you would find footnote 21 or end note 21.

If you could pull that up, Mr. Chase. And that's a reference to Idelson and Blout, correct?
A. Yes, yes.
Q. And Idelson and Blout, you put into evidence today as defendant's trial exhibit 1855, if we could pull that up.

And Idleson and Blout refers to polymers of one amino acid, correct?
A. Yeah. You mean homopolymer.
Q. Homopolymer?
A. Yes, you're correct.
Q. Not a copolymer?
A. You're correct.
Q. And Idleson and Blout say that cleavage is something to be avoided?
A. Yes.
Q. Correct?

A. In essence, they wanted the size distribution that they got on synthesis itself.

(Continued on next page)

Q. And then I think what you said was after you find the Idelson and Blout reference then you keep mining the literature and you find the Nylund reference which was DTX 1965, right?
A. Yes.
Q. And after you look at the Nylund reference, then you're saying that a person of skill in the art then would have been motivated to use the HBr acetic acid step to alter the molecular weight of copolymer-1?
A. What I said, if I may be a little bit more specific, I believe that I did state this in this way, was that by looking at the attempt to avoid cleavage, a person would also, a person of ordinary skill, a person trained in chemistry or peptide chemistry specifically would have understood that one could utilize this as a tool to control the degree of cleavage. Essentially, what I meant was that one needn't come away from an article with a single conclusion. A good scientist, a person with an advanced degree that has the skills that one trains such a person, would come away from reading an article with more than one conclusion. And in this particular case, the conclusion is just as one could go to low temperature, for example, to avoid cleavage, one could go to high temperature to assure cleavage.
Q. Thank you, Dr. Zeigler. So in order to find the claim, the use of -- let me strike that. In order to find the use of HBr acetic acid obvious to controllably cleave copolymer-1 in order

to achieve a molecular weight required the '550 patent, Teitelbaum, Ben-Ishai, Yaron Berger, Idelson & Blout, Nylund and Miller; six different references, correct?

MR. SKILTON: Objection. Misstates the evidence.

THE COURT: Did you follow that, Dr. Zeigler?

THE WITNESS: I believe I did, your Honor.

THE COURT: Can you answer the question?

THE WITNESS: I didn't know whether I was supposed to answer it because of counsel.

A. The answer is yes, this is what our training is, Mr. James. Our training is to look at the prior art and the literature. It's not only patent lawyers that are interested in prior art. Scientists are also interested in it. And therefore, coming up with six papers would not be that unusual for a person that was looking to study and understand what is going on chemically.

Q. Now, let's look at slide 12, please, Mr. Chase. And Dr. Zeigler, slide 12 is a slide that you created based on the internal Teva document that was offered by Mr. Gad, correct?

A. Well, I wouldn't say that we created it. What we did was we, if I may, we just took part of a table and we put it as an inset to another figure that was also included in that document, so we didn't -- in this one, at least, we didn't create anything.

Q. That's fair. All I meant was that you took these, the table and the graph, you took those from an internal Teva

document, correct?
A. That is correct, yes.
Q. And on the lower left, there is a molecular weight distribution curve for four batches of copolymer-1, correct?
A. Yes, that is correct.
Q. And you have never created a molecular weight distribution curve like this using size exclusion chromatography, correct?
A. Using size exclusion chromatography to determine molecular weight?
Q. Yes.
A. You're right.
Q. And these molecular weight distributions, they were generated in 1995, correct?
A. That is the date of the report. I don't know whether or not the experiments were done in 1995. I assume they were done close to 1995, if not 1995.
Q. The report was generated in 1995, correct?
A. You mean the written report?
Q. Yes.
A. Yes, that's correct.
Q. Which is a year after the patent application was filed, correct?
A. I don't know if it's a whole year, but it's, it's a calendar year. Yes.
Q. And just I want to look at the document for a moment, but

just looking at the table in the upper right-hand corner, there are average molecular weights stated for those four batches, correct?

A. I'm not sure whether that's, that has standard deviation results. I'm not sure what "specific" refers to, because the entire table that this came from also discusses standard deviation of the results.

Q. So you don't know what those numbers are in that table you put on the slide, Dr. Zeigler?

A. I didn't say that. I said merely in the row labeled specific, it's a little unclear to me as to what those average molecular weight ranges refer to.

Q. Well, "specific" means specification, right?

A. I guess so. There's a period after it, so -- I suppose. I was not concentrating on that, and perhaps I should have, but I'm not certain as to what that word refers to.

Q. And the average molecular weights that are stated for those four batches, those are peak molecular weights, correct?

A. Yes, that is correct.

Q. So the batches 320, 340, 400 all have peak molecular weights in excess of 10,000 daltons, correct?

A. Are you saying that 320, 340 and 400?

Q. Yes.

A. Yes.

Q. And Teva 03494 has a molecular weight 7,150 daltons, right?

A. Yes.
Q. Let's look at 1704 for a moment. And I just want to look at the introduction, Mr. Chase. And as you understand it, Dr. Zeigler, this paper was written in order to compare batches that were used in the BR 1 trial which was performed between 1980 and 1985, with batches used in a later trial, the 01-9001 trial, correct?
A. That's my understanding.
Q. And if we look at the last sentence of the last paragraph, it says the latter -- and by that it means, current Teva batch, do you see that?
A. Yes.
Q. "The latter was produced according to the up-to-date manufacturing process under GMP conditions and conforms to the same specifications as the drug used in clinical trial 019001 and the drug intended for marketing." Do you see that?
A. I do.
Q. So this paper was really comparing an older set of batches used in the Bornstein trial with a new batch which had a different molecular weight that was used in the 9001 trial correct?
A. Yes. I think we stated that in earlier testimony. I agree.
Q. Let's look at slide 22. And slide 22, Dr. Zeigler, contains your opinions with respect to the '430 patent,

correct?
A. Yes.
Q. And the '430 patent claim 1 has a limitation to over 75 percent of the molar fraction within the molecular weight range from about 2 kilodaltons to about 20 kilodaltons, right?
A. Yes, it does say that.
Q. And that's a description of the molecular weight distribution, correct?
A. Yes.
Q. And the '550 patent does not disclose a molecular weight distribution for any copolymer, correct?
A. Yes, that's correct.
Q. And there's no reference in the '550 patent to any percentage of molecules on a molar fraction basis, correct?
A. Yes, that is correct.
Q. And there's no data in the '550 patent from which you could calculate the molar fraction of a copolymer-1 sample, correct?
A. Yes, that is also correct.
Q. The '430 patent also contains a limitation to a trifluoroacetyl copolymer-1 having over 75 percent of its molar fraction within the molecular weight range from about 2 kilodaltons to about 20 kilodaltons, do you see that?
A. I do, yes.
Q. Now, you didn't talk about that in your direct examination, did you?

A. That's correct.
Q. But there's nothing in the '550 patent about the percentage of molecules of the trifluoroacetyl copolymer-1 molecules in the '550 patent, right?
A. Just as there is nothing as we mentioned just previously with regard to the fully deprotected product.
Q. In fact, there's nothing in the prior art to the patents in suit that would provide you with data from which you could calculate the molar fraction of the copolymer-1 molecules claimed in the '430 patent, correct?
A. In terms of calculations, that is correct. I was referring to the expectations of somebody that had some knowledge of the polypeptide synthesis field, but what you're saying is correct.
Q. Okay, let's talk about the expectation that you set forth in this slide. Again, it's in the lower right-hand corner. And you discuss the fact that your expectation is based on the substantial overlap in the molecular weight distributions, right?
A. Yes, but not entirely. In other words, the statement here, basis for obviousness, is apparently restricted to the 320, 340 and 400 and to some extent I miswrote, because I was using that more to support the expectation that somebody who has read the publications in the field would have come to.
Q. Well, the publications that were available in the field, they didn't provide a molecular weight distribution for

copolymer-1, correct?
A. Yes. The distinction I'm making is not copolymer-1, but a polypeptide produced by polymerization of N carboxyanhydrides. It's a distinction. I'm not disagreeing with you.
Q. So it's your opinion, Dr. Zeigler, that a person of skill in the art could have made copolymer-1 using the prior art methods and have measured its molecular weight distribution, is that your testimony?
A. Could you go through that one more time?
Q. Yes.
A. I mean, I understood the words, but I just want to make sure that I'm very clear in terms of how you phrase it.
Q. I think we've established that there were no data in the prior art to the patents in suit from which you could calculate a molar fraction for copolymer-1 molecules, correct?
A. That's my understanding.
Q. And so your only basis for an expectation that there would be a substantial overlap as stated on this slide are the batches that were used in the Bornstein trial and Figure 2, which were not available to the public, correct?
A. Figure 2 is not available to the public, and Bornstein did not have a specific distribution as part of the paper.
Q. So there was no basis for a person of skill in 1994 to have calculated the percentage of molecules on a molar fraction basis between 2 kilodaltons and 20 kilodaltons, right?

A. Calculation, that is correct.
Q. Well, the claims are related to calculations, right?
A. Yes.
Q. If you look at slide 23, Dr. Zeigler, you have your opinions there with respect to claims 2 and 3, right?
A. Yes.
Q. And they have specific time and temperature limitations for the HBr debenzylation step, right?
A. Yes.
Q. But those specific times and temperatures, they're not found in the '550 patent, correct?
A. That is correct.
Q. If we could, I'd like to go back just for a moment to the Teitelbaum paper and I believe you testified that the time and temperature for the Teitelbaum reaction was provided by the Yaron and Berger reference.
A. First of all, that's for the HBr deprotection of benzyl esters.
Q. Yes, I misspoke.
A. You didn't misspoke. I just wanted to focus on being specific and a correct answer.
Q. We could look at that together just for a moment.
A. Surely.
Q. Let's pull up 1934. Before we do that, Mr. Chase, let's leave that up, just for a second. So the Teitelbaum 1971

paper, Doctor, describes the deblocking of the carboxy groups of the glutamic acid with the hydrogen bromide in glacial acetic acid, right?

A. Yes.

Q. Then I think we went through a moment ago that you looked through Ben-Ishai, a cite cited there, cite 16 and you find the Yaron and Berger reference, which is DTX 1934 and you said that gives the time and temperature, correct?

A. The Yaron and Berger?

Q. Yes.

A. As I mentioned, they wanted to avoid peptide cleavage, and they report that what they did was vary the time and temperature.

Q. Right, and you said that the time and temperature stated there was room temperature overnight, right?

A. That was the Ben-Ishai and Berger paper. I'm not sure whether you're talking about the Yaron and Berger paper or the Ben-Ishai and Berger paper. Yes, to the best of my recollection, the Ben-Ishai and Berger paper was in one place it said 12 hours, in another place it said overnight, and room temperature.

Q. Okay. Just give me one moment to look at this, because I don't want to mislead you.

(Pause)

Q. I apologize, I have it now. Could you pull up 1759,

Mr. Chase? 1759 is the Ben-Ishai article, correct?
A. Yes.
Q. And let's look at the last, next to the last page, Mr. Chase, where it talks about the hippuric acid in the middle of the page right there. It says, "To benzyl hippurate there was added hydrogen bromide in glacial acetic acid and the mixture was left overnight at room temperature." Do you see that?
A. I do.
Q. And you testified that that would provide you with the time and temperature for the Teitelbaum 1971 HBr debenzylation step, correct?
A. Yes, that's the reference that I, I don't know if I stated it exactly in that way. What I said, though, was that if one wanted the details for debenzylation, one would have gone to Ben-Ishai and Berger.
Q. And these are the details for the debenzylation in Ben-Ishai and Berger, right?
A. Yes, they are, right.
Q. When you carry out the debenzylation as set forth in the 1971 Teitelbaum paper, you get a molecular weight for copolymer-1 of 23,000, correct?
A. That is correct, yes.
Q. So when you follow the directions in the 1971 Teitelbaum paper with respect to time and temperature of the HBr

debenzylation step you get a molecular weight of 23,000, right?
A. Well, Teitelbaum, et al, did. Again, there could be batch-to-batch variation. I talked a lot about that. But in terms of that particular paper, and in terms of the '550 patent citing that, that's correct, that leads to a molecular weight at least of those two batches of approximately 23,000.
Q. Thank you. So let's look at slide 24 now, Mr. Chase. Slide 24, Dr. Zeigler, is your analysis of the '476 claims, right?
A. Yes.
Q. And in the '476 claims, you have the molecular weight limitation for the molar fraction between 2 and 20 kilodaltons and you also have a limitation that it contains less than 5 percent of species of copolymer-1 having molecular weight over 40 kilodaltons. Do you see that?
A. I do.
Q. And on the right, you say "Cop-1 made by the '550 patent, e.g., 10 to 15 kilodaltons, will have only a small molar fraction, if any, above 40 KDa." Do you see that?
A. I do.
Q. But in fact, the evidence in this case shows that that is not the inevitable result if you have a copolymer-1 batch with a molecular weight between 10 and 15, right?
A. Yes, it depends how you look at the glass being half empty and half full.

Q. So in fact, you're aware that there are batches in evidence right now between 10 and 15 kilodaltons that have greater than 5 percent species over 40 kilodaltons, right?
A. Could you give me specific examples?
Q. Well, they're in the patents, right? They're in the patents in suit?
A. Oh. The 5 to 9 kilodaltons talks about having no material above 40 kilodaltons --
Q. You're talking about --
A. -- so I'm a little confused.
Q. -- material between 12 and 14 kilodaltons here, correct, Dr. Zeigler?
A. Yes.
THE COURT: Mr. Skilton, you have an objection?
MR. SKILTON: Yes, he's interrupting the witness.
THE COURT: If you can --
MR. JAMES: I apologize, your Honor.
THE COURT: Yes, let him finish. It's a little difficult with both of you going back and forth.
Q. Dr. Zeigler, do you have the '808 patent there?
A. That would be number 1?
Q. Yes, and Mr. Chase, could we look at column 3? Just before the heading example 2?
A. And where are we?
Q. I have it on the screen. Column 3 lines 14 through 18. Do

you see that?
A. Yes, I do.
Q. It says the other batch of copolymer-1 which was not subjected to chromatography had an average molecular weight of 12 KDa. Do you see that?
A. I do.
Q. And that would be between 10 and 15 as listed on your slide, the one we were just looking at, right?
A. Yes.
Q. And this says that 2.5 of the batch had a molecular weight above 42 kilodaltons, do you see that?
A. Mm-hmm.
Q. And 5 percent of the total copolymer-1 species in the batch had a molecular weight over 40 kilodaltons. Do you see that?
A. I do.
Q. So you would agree with me, Doctor, that is not a necessary result, that if you have a molecular weight of between 10 and 15 kilodaltons that you will have less than 2.5 percent or less than 5 percent species over 40, correct?
A. No, Mr. James. This is talking about specifically 12 kilodaltons and we're talking about in excess of 10,000 daltons, and therefore your statement is not absolutely correct.
Q. But you would agree with me that a batch that had a molecular weight of 12 kilodaltons as shown here has greater

than 5 percent species over 40 kilodaltons, correct?
A. This particular batch, yes, but not necessarily, but again, I would not go down to in excess of 10 because I haven't seen such data.
Q. But we -- strike that.
A. I'm trying to be specific. Not difficult.
Q. Let's look at slide 27, please, Mr. Chase. Slide 27, Dr. Zeigler, relates to your analysis of the '539 claims, right?
A. Yes, it does.
Q. And claim 1 of the '539 patent claims a copolymer-1 composition that has a molecular weight of about 4 to about 9 kilodaltons, right?
A. Yes.
Q. And that's a peak molecular weight measured using size exclusion chromatography, right?
A. Yes.
Q. Then it says that the composition is suitable for treating multiple sclerosis. Do you see that?
A. I do.
Q. Now, Dr. Zeigler, you offered an opinion that that claim was obvious over to the '550 patent, right?
A. I did, yes.
Q. The '550 patent does not disclose a copolymer-1 batch having an average molecular weight of about 4 to about 9 kilodaltons, right?

A. Would you please just repeat that question? I lost my concentration for a moment.
Q. The '550 patent does not disclose a batch of copolymer having a molecular weight of about 4 to about 9 kilodaltons as the Court has construed that term, right?
A. That is correct.
Q. But you offered the opinion that it would be obvious to use that copolymer-1 having those molecular weight characteristics to treat a patient who had multiple sclerosis, right?
A. That is my opinion.
Q. But you're not a medical doctor, correct?
A. That is correct.
Q. And you have no experience treating people for multiple sclerosis, right?
A. Yes. I thought that this was about somebody of ordinary skill in the art, and I answered this according to that.
Q. Well, you have no basis to testify as to what a person who was treating multiple sclerosis would have believed about batches of copolymer-1 in 1994, correct?
A. If I was relying strictly on my own abilities, that might be correct, but I was relying on the Bornstein paper specifically.
Q. You were relying on the 1987 Bornstein paper that reports a clinical trial for copolymer-1 having molecular weights between 14 and 23,000 daltons, right?

A. That is correct, yes.
Q. And on the basis of that paper, you offered the opinion that you thought it would be obvious to treat a patient with a copolymer-1 batch that had a much lower molecular weight, correct?
A. I think that we have to understand here that I am not advocating how a physician would treat a patient. I am looking the patents of a person of ordinary skill in the art as I defined it, and therefore, I made an attempt to answer it from that perspective. I'm not a physician, I have no intention of injecting any people with copolymer-1 or anything else. But nonetheless, I feel that a person of ordinary skill in the art could offer an opinion on that.
Q. A person of ordinary skill in the art as a biochemist?
A. And polymer chemist.
Q. And polymer chemist, you believe it would be appropriate to offer the opinion about whether or not it would have been obvious to treat people with multiple sclerosis with a new copolymer-1 composition?
A. That was what I was asked to do. I felt confident doing it then. I feel confident doing it now. I'm sure that the Court is going to make a decision on that.
Q. And you're aware that after the Bornstein trial on the copolymer-1 having molecular weight between 14,000 and 23,000, that Teva had to carry out another clinical trial on the low

molecular weight copolymer-1, right?
A. I know that there were other clinical trials. Again, the specifics of it, you know, are not ingrained in my memory, but I know that there were other trials. I believe three, four years later, something of that sort. I think probably the '91-'92 trials are what you're referring to.
THE COURT: Mr. James, how much longer, approximately? And/or is this a good time to break?
MR. JAMES: This would be a good time to break. I would say 30 minutes at the most.
THE COURT: We'll take a ten-minute break.
(Recess)
THE COURT: All right, Mr. James.
MR. JAMES: Thank you, your Honor. Mr. Chase, could we put up slide 19 again, please?
Q. Dr. Zeigler, let me go back again to your opinion on obviousness of the claims of the patents in suit and with respect to the '808 patent, it's your opinion that the '550 patent renders obvious the claim to a copolymer-1 composition that has a molecular weight of about 5 to 9 kilodaltons, right?
A. Based on knowledge of the kinds of molecular weight profiles that one would get with N carboxyanhydrides polymerization, yes. Not specifically necessarily for copolymer-1, but just in general.
Q. Well, you've offered an opinion that this claim directed to

copolymer-1 having that average molecular weight limitation is obvious, right?
A. Yes.
Q. So it's your opinion that a person of skill in the art could have followed the teachings of the '550 patent and the other references and have made copolymer-1, correct?
A. Yes.
Q. And that they could have targeted this molecular weight range of about 5 to 9 kilodaltons, right?
A. Yes, by manipulating time and temperature.
Q. And they could have adjusted the HBr debenzylation conditions in order to achieve that molecular weight, right?
A. That is my position.
Q. And that they could have used the techniques known in the art at the time to determine whether in fact the sample had a peak molecular weight between 5 and 9 kilodaltons, right?
A. Using SEC and calibrants?
Q. Yes.
A. No, that's not my position. I don't believe that there were suitable calibrants, you're talking about the '550 patent. No, not by that SEC chromatography.
Q. So it's your opinion that they could have made the product but they could not have determined its molecular weight in 1994, correct?
A. That's not -- no, that's not my opinion. My opinion is

that there were many ways, particularly direct methods of measuring molecular weight that were available by 1994. I'm sorry, I thought you were talking about the '550 patent in terms of 1994. I'm not nearly as certain about the calibrants at 1994 as I am about the '550 patent. So maybe I misunderstood you, but there's certainly one thing I know because it's true also at the time of the '550 patent is that there were a number of ways of measuring molecular weight.

Q. But the Court has construed the claim to require the peak molecular weight measured using SEC, correct?

A. Yes. I'm not trying to cross the Court in any way, shape or form, merely to state that there were and both in terms of the '550 patent and the '808 patents and patents in suit, there were methods that were available to measure molecular weight. I myself would have been most comfortable using those because of my own experience and because of my own preferences.

Q. You've offered the opinion that this claim is obvious, correct?

A. I did, yes. And I do.

Q. So my question is, Dr. Zeigler, you believe that a person of skill in the art after they made this copolymer-1 composition according to the method you said was obvious that they could have measured its molecular weight in a way that would have met the Court's claim limitation of average molecular weight, right?

A. Insofar as the direct measurements are related to the peak average, in other words, they have to be related to some degree. That's what I'm counting on. That's the basis on which I am opining. What you're saying is partially correct in the sense that I am not opining in terms of SEC and calibrants, that's beyond my area of expertise. I've never done that. But I am opining on the general use of molecular weight determination, which obviously the Court is not defining copolymer-1 on.

Q. Let's go back to slide 19. Dr. Zeigler, in the middle of the right hand column where you say basis for obviousness, there is a reference to EP 620 and you say it discloses copolymer-1 like compositions as low as 5 kilodaltons. Do you see that?

A. I do.

Q. Now, you understand that the '620 patent was considered by the Patent Office during the prosecution of the patents in suit, correct?

A. I assume so. I have no way of knowing, Mr. James. Again, this is beyond my expertise and ken. I assume so, because it's part of the prior art.

Q. Well, I can show you the face of the patent. The face of the patent shows that the EP 620 application was considered by the Patent Office.

A. That's fine.

Q. So you disagree with the Patent Office's issuing these patent claims over the '620 in combination with the '550, correct?

MR. SKILTON: Object to relevance.

THE COURT: True. Next question.

Q. Now, let's look at the Court's construction of the term copolymer-1. Have you looked at that, Dr. Zeigler?

A. Yes, I've seen that.

Q. And in particular, the Court has construed the term copolymer-1 as a mixture of polypeptides having certain characteristics and if we go down to the bottom it says, "which is synthesized by polymerization of suitably protected amino acid carboxyanhydrides." Do you see that?

A. I do.

Q. Now the '620 patent application, EP 620, that does not disclose polymerization using amino acid carboxyanhydrides, correct?

A. I was very careful not to mention EP 620 to indicate this is a methodological biological approach to produce what they hoped to be copolymer-1 like polypeptides.

Q. Let's go back to slide 19. In fact, Dr. Zeigler, the EP 620, it doesn't disclose copolymer-1 compositions with an average molecular weight of 5 kilodaltons, does it?

A. I'm not sure what section you're referring to, but if you recall I was quoting a sentence on the front page to the effect

that this was the range that the patent was disclosing, so I'm not quite sure the distinction that you're making, Mr. James.

Q. Well, let's look at the 620. It's DTX 1970. Do you have that, Dr. Zeigler?

A. It's on my screen. I haven't gotten a tab.

Q. And in particular, I'd like to look at page 3, Mr. Chase. The second full paragraph towards the end, I believe it's the sentence you were referring to, right, Dr. Zeigler, it says, "More specifically, a preferred copolymer may consist of alanine, lysine, glutamic acid and tyrosine and have a molecular weight between about 5,000 and 50,000 daltons." Do you see that?

A. I do.

Q. Those molecular weights, 5,000 and 50,000 daltons, those are individual molecular weights, correct?

A. One could understand it that way, but one can understand it in a way that's very different. Because the original production of clones of bacteria include billions of clones of bacteria with billions of different individual sequences and sizes and therefore it really depends if you're talking about the entire range of materials produced, or the final objective of getting down to one or a few sizes. So that's not clear at all to me. It could be either one, and certainly in one case I would be right, and in one case you would be right. It just, it's in the eye of the beholder.

Q. Dr. Zeigler, the reference to 5,000 and 50,000 daltons, those are references to individual molecular weights of polypeptides, correct?
A. Not necessarily. Molecular weight could be average molecular weight as well. I think that it's open to question, since in the process one starts with a production of products with a large range of molecular weights which would be average molecular weights. In the course of carrying out the patent, one could reduce the diversity but one doesn't have to. Therefore, it seems to me with an honest reading that it could be individual single units or it could be the averages, depending at what point in the process you were looking at.
MR. JAMES: Your Honor, if I could hand up the deposition transcript, please?
THE COURT: Sure.
Q. Dr. Zeigler, and, your Honor, I'm going to ask him about the transcript page 26, lines 21 to 25.
A. What pages did you say again, please? 26?
Q. Yes, sir.
A. Yes.
Q. Lines 21 to 25.
THE COURT: Go ahead.
Q. Dr. Zeigler, at your deposition --
A. Excuse me, I'm not sure, it says at one point page 101 and another place at the bottom it says page 26. So I'm not sure

which page you're referring to.
Q. In, each of the pages has four quadrants, do you see that?
A. I do.
Q. And in the upper left hand quadrant there's one that says page 26.
A. Yes.
Q. Do you see that?
A. Yes.
Q. And do you recall I took your deposition? Dr. Zeigler, do you recall that?
A. Yes, I -- it certainly is familiar to me.
Q. Do you remember that? Okay. And at your deposition I asked you the question:
"Q. And the reference to 5,000 and 50,000 daltons, those are references to individual molecular weights of polypeptides, correct?
"A. Yes."
Is that your testimony, Dr. Zeigler?
A. No, it seems to me that right after -- I'm on page 27, what I did was, I expanded the answer there saying each copolymer, that is, each vector that is used to get into the bacterium, each one has got a particular molecular weight, and that's what I'm saying right now. In other words, if one starts off and then clones the various sequences and sizes, one would get a composition in bacteria of billions of different vectors and

clones, and again, one can understand the product of this mixture of different bacteria as producing peptides, polypeptides of an average molecular weight, but ultimately, one could by virtue of cloning smaller and smaller numbers of colonies get to smaller molecular weights.

If I didn't say that, that's certainly what I meant.

THE COURT: Dr. Zeigler, do me a favor. Going forward, just answer his question. And then when Mr. Skilton gets up, he'll ask you some additional ones and you can respond to that. Okay?

THE WITNESS: I'm sorry.

THE COURT: No, that's all right. Don't apologize. Go ahead, Mr. James.

MR. JAMES: Thank you.

Q. Dr. Zeigler, still focusing on that sentence that we're looking at in the 620 EP, there's no reference in that sentence to average molecular weights, correct?

A. That is correct.

Q. So you would agree that -- well, strike that.

Dr. Zeigler, there's no disclosure in the '620 patent of the measurement of an average molecular weight using size exclusion chromatography, correct?

A. Yes, that is correct.

Q. And the authors of the '620 patent, they were focused on polypeptides that had molecular weights of 15,000 to 23,000

daltons, correct?
A. If I may correct a minor point. There's one author. I believe it's just Dr. Cook.
Q. Thank you.
A. But with that minor adjustment, I believe that that is stated somewhere at the beginning. I would have to look to find it.
Q. It's stated in the application that the focus was polypeptides between 15,000 and 23,000 daltons, correct?
A. I remember reading that somewhere in the patent.
Q. And in fact, the two molecules that are exemplified in the 620 EP, they have molecular weights that are 11600, and 16,900, correct?
A. I remember that. I'll take your word for it as to the exact molecular weights. It certainly sounds like the results. I'm sure you're right.
Q. There is no example in the '620 application of a polypeptide that had a molecular weight of 5,000 daltons, right?
A. Correct.
Q. And you would agree, Dr. Zeigler, that you can't identify an example in the prior art to the patents in suit to a copolymer-1 having an average molecular weight of 5,000 daltons, correct?
A. That is correct. You're talking about average molecular

weight, I believe, in that last question, right?

MR. JAMES: Yes.

I have no further questions.

THE COURT: All right. Redirect.

MR. SKILTON: Thank you, your Honor.

THE WITNESS: Thank you, Mr. James.

MR. JAMES: Thank you.

REDIRECT EXAMINATION

BY MR. SKILTON:

Q. Dr. Zeigler, it's been a long day for everybody, so I'll try to direct you specifically to the subjects, and if you could keep your answers relatively short.

A. It's very difficult for a pedantic teacher.

Q. Yes, indeed. Nick, will you pull up the '550 patent? And I point you to column 1, line, I think it's 57. All right, now, Doctor, you were asked about this particular line. Is copolymer-1 as you read that paragraph one of the novel compositions disclosed in the '550 patents?

A. Yes, it is.

Q. And the disclosure there includes the 10,000. How did you in your analysis as a person of ordinary skill in the art regard the significance of that disclosure in terms of your opinions, the 10,000.

A. The way that I read it, and I was reading it I guess every time as a person of ordinary skill in the art rather than as a

patent lawyer looking for claims versus specifications, was that each of these molecular weights by virtue of being mentioned could be applied to copolymer-1 batch.

Q. Nick, would you pull up PTX 17 for me, please? Your Honor, it was admitted in the first case. In particular page 304384 from that, and second full paragraph, if you would. And, Dr. Zeigler, I will represent to you that this comes from a part of Teva's patent prosecution statements to the United States Patent Office. The one I want to point your attention to is the first sentence, and would you highlight that? And I will read it. "The '550 patent teaches a copolymer-1 with a minimum molecular weight of 10 kilodaltons." Doctor, how does that statement to the United States Patent Office comport with your opinions?

A. It seems to support the way that I read it. As I mentioned, I'm reading it as a scientist.

Q. Now, Doctor, we talked about the trail that you were talking about in your direct, and Mr. James directed some questions on the combination of articles that you referred the Court to. But I want to address you in that regard to a more specific aspect as it relates to the HBr cleavage step. What is the chemistry taught to the person of ordinary skill in the art should they have those articles or any one of them in combination tacked to their board as they're doing the HBr cleavage in this experiment, what is the chemistry taught?

A. As I defined a person with ordinary skill in the art, an advanced degree, I would expect them to understand that HBr cleavage of peptides depends on the conditions that are being employed. And that one can employ conditions of lesser stringency in order to avoid peptide cleavage or conditions of greater stringency or harshness in which case one can accelerate the amount of cleavage.

Q. Now, in his lengthy cross as it relates to molecular weight and the Figure 2 and the like that you used and cited in your opinions as they relate to the patent claims in question, Mr. James did not mention the concept of polydiversity -- poly -- help me on that, I'm getting tired too.

A. Dispersity?

Q. Thank you, throughout those questions, focusing on such things as peak molecular weight and the like. Would you take the opportunity to relate your testimony earlier today on polydispersity and as it relates to ranges and the question of peak molecular weight, and I'll first ask you this question: Does the determination of peak molecular weight in any given sample as respect to the molecule, does that in any way affect questions of polydispersity?

A. Mr. Skilton, could you either repeat the question or rephrase it? I'm not sure I understand what --

Q. I'll try again, because it was a terrible question.

A. I'm sorry.

Q. So bad that I don't understand it.

How does the question of polydispersity relate to this issue of what you can expect with respect to adjacent ranges?

A. Virtually every method of measuring molecular weight will give somewhat different results, and consequently, one could get an idea of the degree of polydispersity by employing different ways of measuring molecular weight, but one would hope that the peak molecular weight would not be, using suitable calibrants would not be too far away from the other molecular weight determinations that you use, and having said that, understanding that there is such great diversity in the sizes, they could be different, but one would hope that they wouldn't be so different.

Q. All right, then, how does your opinion that you developed this morning on overlap relate to the question of expectable performance with respect to the issue of poly dispersity? Do you understand what I'm asking you?

A. Yes, I believe I do. I think that again, without using the Gad report as prior art, what I was using it was as just kind of a general means of looking at differences in peak molecular weight as related to the degree of the percent of molar overlap, that the degree of overlap is really extensive and it becomes more extensive, the overlap, as the peak molecular weights become closer and closer between two batches.

Q. Let's stay within the peak concept as was being framed by

Mr. James. Does the molecular weight distributions of copolymers within a peak of 9 versus a peak of 10 have overlap?

A. I think that anybody with experience in poly disperse solutions would feel that there would be a tremendous degree of overlap.

Q. Tell me, does your experience, how does your experience with similar molecules to copolymer-1, and identify them, please, for the Court in the answer, permit you to make the, give the opinions you did with respect to obviousness, for example, at a 5 to 9 range?

A. The materials that I was making which was polymers of sequential peptides, again, would have a considerable diversity and 9 and 10 would have considerable overlap.

In fact, I'm not quite sure to what extent one would be able to fractionate because there's an inherent error in the measurement which also has to be taken into account.

(Continued next page)

BY MR. SKILTON:

Q. Now, nobody wants me to go over any of the slides again, including myself, but you were asked a lot of questions specifically about certain limitations.

As a first general proposition, given the questions that Mr. James was asking you, has your opinion on any of these obviousness questions that we addressed in the slides changed in any respect?

A. No, Mr. Skilton. Because I was looking at this not as a patent lawyer. I've been looking at that -- in fact, the reason I was brought in was strictly in terms of my scientific opinions, and I certainly hope not for my legal opinions. That's not my --

Q. Well, let me drill down a little bit to focus you and the Court on what I'm trying to get at; and that is to say that you mentioned in response to Mr. James that time and temperature variations to you were obvious, and as a person of ordinary skill in the art.

And so we talked about particular, if you will, statements of time or temperature. You opined that they were obvious. Could you fill that out? What is the basis for you to say to the Court as person of ordinary skill in the art, that the specific kinds of time and temperature limitations that are now claimed in the patents were, in your opinion, obvious to one of ordinary skill in the art?

A. Virtually any chemical reaction will have its rate depend on time and temperature.
Q. And?
A. That's inherent in terms of chemistry.
Q. And what is also, in your opinion, inherent in terms of variations of that time and temperature condition when you're talking about, for example, the HBr step?
A. Certainly the amounts that are mentioned in '808 in the patents in suit, but again I don't see any need to be confined necessarily. A priori as a scientist looking to study cleavage, I wouldn't necessarily think that one is confined to the particular range that's specified there.
A reasonably good scientist will have an open mind about that, and, and test the variables.
Q. All right. And again without getting back to the specific slides, we talked about limitations that talked about the constituency in 5 percent and 2 percent and over 40, et cetera. And I don't want to specifically identify the terms per se, but you also opined that those limitations were obvious to you as one of ordinary skill in the art. Did I understand that correctly?
A. Yes. I stand by those opinions.
Q. And, again, at the high level, if you will, of 30,000 feet, explain to the Court the basis for your opinion as a person of ordinary skill in the art as to why these limitations, in terms

of constituency, were obvious?
A. It was my expectation, it still is my expectation, that the degree of overlap in such a polydisperse system as peptide polymerization would be extensive as long as the molecular weights, however determined, were reasonably close.
Q. And from your experience with other like molecules, can you tell the Court, a little more specifically, as to why you had that opinion?
A. In my experience, that kind of diversity occurred with the polymers that I was studying, and just like any other person of ordinary skill in the art, I would utilize that background and experience to a system that I haven't studied specifically. That's the nature of what research is all about.
Q. And with respect to the polydispersity of the molecules you were working with, did you consider them in contrast, for example, to what you understood was the polydispersity of co-polymer-1?
A. Would you please repeat that?
Q. Is there any similarity, in your opinion, between the polydispersity of the molecules that you were working with and the polydispersity of copolymer-1?
A. There were some similarities in terms of wide distribution of molecular weights, but the molecular weights of the monomers were certainly different.
Q. Now, I want to talk specifically, if I may, to the exhibit

that relates to the Weizmann batches.

MR. SKILTON: Your Honor, may I consult with my colleague for just a second, please?

THE COURT: Yes.

MR. SKILTON: Thank you.

Your Honor, I'm now referring the Court again and the witness to DTX 1704R.

And, Nick, would you turn to the portion of the document that the witness was earlier looking at, which relates to the molecular weight batches from the Weizmann Center.

Q. And, first of all, let me try, if I can, to understand what your answers were to Mr. James.

You list this document, amongst others, as support for your opinion; am I right?

A. Yes. It's pretty clear that it's not prior art per se. You it was not available to the public.

Q. Well, with respect to the Weizmann batches, you did indicate, did you not, that they were produced, according to your study, this document sometime in the early '80s?

A. Yes.

Q. Okay. Now, was cop-1 of the molecular weights of 10,350, 13,000 and 14,000 kilodaltons known in the art as of the date of May 24th, 1994?

A. Well, certainly 14,000 was disclosed in the, excuse me, in the Bornstein paper.

Q. And is there anything, in your opinion, about these profiles that are shown in the document that we're looking at, that's unexpected about the molecular weight profiles therein shown for those three batches?
A. No. They conform, and I believe that Dr. Gad concludes that to the specification that, that were accepted at the time of preparation.
Q. And would you expect batches in the ten to 15 kilodalton range to have a high percentage of its molar fraction within the two to 20 kilodalton range?
A. I would, based on my studies of poly dispersed solution of polypeptides.
Q. And would you expect batches in the ten to 15 kilodalton range to have material over 40 kilodaltons? Would you expect a small amount of that material above 40 kilodaltons to be in the range? And that's a very bad question and I'm going to try again.

What would you expect with respect to the amount of material that would be over 40 kilodaltons?
A. I can't say specifically, Mr. Skilton, because every batch is going to produce a different distribution of molecular weights, and so I'm not sure that I can really answer that question, except to say that if it's in a molecular weight range that you're talking about, it will be low.
Q. All right. Now, what about these three batches, the

Weizmann Center batches?

MR. SKILTON: Nick, would you please pull up the slide that relates to this question?

All right, Nick, would you go back to figure B., please, and expand the part around the 40,000? Sorry, your Honor, for the imprecision of this.

THE COURT: That's okay.

Q. All right. Now, we're looking at that portion of this expanded, you see that? And, Doctor, comment on that 40 kilodalton range and how it meets your expectation based on what you know about polydisperse?

A. Yes. I'm sorry. Each of the hash marks here represents 10,000 daltons molecular weight. So this hash mark would be 10,000, this would be 20,000, this would be 30,000, this hash mark would be 40,000 molecular weight, and this hash mark would be 50,000 molecular weight.

Q. And as a person of ordinary skill in the art, does that polydispersity as represented on these batches, in any way surprise you?

A. It doesn't surprise me.

Q. Is it consistent with your expectations?

A. In the sense that it would be low.

But, again, there's no way for me to know, Mr. Skilton exactly what sort of distribution would be over 40,000 except just to tell you that, that molecular weights in the ranges of

these four batches should have a very reasonably low, because there's a wide distribution of molecular weights, but there's a limit.

I'm not surprised, however, that we are dealing with an extremely low percentage of molecular weights, multi fractions in the 40,000 molecular weight.

Q. All right. So now convert the explanation you gave with respect to those curves with respect to those batches?

A. In this particular case, these four batches of Dr. Gad, all have less than 40,000 molecular weights, that is in terms of significance.

There's no significant amount of material. There could be a few molecules, but not a significant percentage of the molar fraction. In fact, it looks to me like all of them hit zero before they hit 40,000.

Q. And how did the observation you're making on this chart, then, support the opinions that you gave with respect to the obviousness of the claims, for example, identify the 40 kilodalton and above range, how does that analysis support your opinion?

A. Well, my opinion is that the amount of material that is in that range is going to be extremely low, if in fact the molecular weight, if you will, by peak average is in the low range, say ten to 15,000 molecular weight.

MR. SKILTON: Now, your Honor, I'm going to do

something, with the Court's indulgence, that I don't normally do. But since it's a trial to the Court, I'm going to ask the witness, is there a question I should have asked you but didn't, to clarify your testimony?

THE COURT: Go ahead. Is there?

Q. Doctor, you were cross-examined for about two hours, roughly. In the course of that examination, Mr. James asked you a number of questions. I tried to follow up.

And my question that the Court has permitted me to ask or perhaps ask you directly, is there a question that you would like me to address to you that you think you would like to clarify?

A. What's for dinner?

THE COURT: Okay. Thank you, Dr. Zeiger.

Anything further from plaintiffs?

MR. JAMES: No, your Honor.

THE COURT: All right, thank you very much, Doctor, you're excused.

THE WITNESS: Thank you, your Honor.

(Witness excused)

THE COURT: All right. Who is our next witness?

THE WITNESS: Your Honor, may I carry these back?

THE COURT: You don't have to. People will come and get them.

THE WITNESS: Can I leave the laser pointer?

THE COURT: You can leaver whatever you want. That would be great. Thank you.

MR. JONES: Your Honor, the next witness is Doctor Susan Rice. I anticipate her testimony will go, especially if I talk slow like I'm supposed to, about an hour to an hour and 15, hour 20.

With the Court's indulgence, I know it's been a long day for everyone. And, frankly, Dr. Rice has a bit of head congestion. If we could get here in, get her tendered as an expert, and then call it a day and pick her up tomorrow morning, if that's okay with the Court?

THE COURT: You can do that. Come on up.

MR. JONES: Is that acceptable?

MR. WIESEN: That's fine. No problem.

MR. JONES: Thank you, your Honor.

THE COURT: Come on up, Doctor.

MR. JONES: With that understanding then, Dr. Rice, please.

SUSAN A. RICE,

called as a witness by the defendant,

having been duly sworn, testified as follows:

DIRECT EXAMINATION

BY MR. JONES:

Q. Would you please provide the Court with your educational background?

A. I have a bachelors of science in biochemistry from the University of California at Davis. I received that in 1971. I have a Ph.D. in comparative pharmacology and toxicology, also from the University of California at Davis. I received that degree in 1976.

Q. Dr. Rice, I'm going to have you explain what pharmacology is, briefly?

A. Pharmacology is a science that studies the efficacious or therapeutic effects of drugs.

Q. And then can you tell us what toxicology is?

A. Toxicology is a science that studies the adverse effects of drugs, chemicals, physical agents, such as radiation.

Q. Now, I believe you said your Ph.D. was in comparative pharmacology and toxicology, correct?

A. Yes, it is.

Q. Why don't you tell me what the term comparative adds to your degree; what is that denoting?

A. Comparative in this case means comparative species. Many toxicology and pharmacology programs are centered completely around the human experience.

My program included all sorts of animal species, in addition to humans. So we studied the biochemistry, the physiology, pharmacology, and toxicology of multiple species from mice, rats, dogs, horses, and humans.

Q. Did you prepare a thesis to obtain your Ph.D.?

A. Yes, I did.
Q. What did you do your thesis in?
A. My thesis was on the pulmonary edema caused by the thiocarbamide, which is also known as thiourea.
Q. I've never understood any Ph.D.'s thesis, so I'm going to ask you to translate that as well. Could you tell me in lay person's terms what you did, what you wrote your thesis on?
A. Thiourea was used as a rodenticide. It killed rodents, primarily rats. And my thesis involved looking at the mechanism of action of that rodenticide and determining why it caused pulmonary edema, which means essentially water in the tissues of the lung.
Q. Can you tell me what toxicity is and how it relates to toxicology?
A. Toxicity is actually the adverse effects that are seen. And toxicology is the science that studies adverse effects. And part of the science is involved in looking at the dosage, dose response, absorption, distribution, metabolism, secretion of drugs, chemicals and their metabolites and looking at their effects in various organs in the body.
Q. Dr. Rice, what did you do after you received your Ph.D. in 1976?
A. I took a post doctoral position at Stanford University in the School of Medicine, the Department of Anesthesia.
Q. What was the focus of your post doctorate work?

A. In my post doc, I studied the toxicity of the inhaled anesthetic agents. And by inhaled I mean such things ass ethyl ether, which is only an example of a very old anesthetic, but most people recognize it.

Q. What did you do following your post doctorate work at Stanford?

A. I stayed at Stanford, and I was a research associate for a period of two years. And during this time I also studied additional toxicity of the inhaled anesthetic agents.

Q. Were you ever given an opportunity to join the faculty at Stanford University?

A. Yes. In 1979 I joined the faculty as assistant professor, in the Department of Anesthesia, School of Medicine.

Q. Did you receive any promotions while on the faculty at Stanford University?

A. Yes. I was promoted to associate professor.

Q. During your time at Stanford University as assistant, then an associate professor, what was the focus of your research work?

A. The focus of my research continued to be various aspects of the toxicity of the inhaled anesthetic agents. I worked both with animal models and with in vitro systems to look at the toxicity, and I participated and designed clinical studies with my M.D. faculty colleagues to look at issues in humans.

Q. You're going to talk about it a little more later, but

would you just briefly explain the difference between an in vivo test and an in vitro test, at least as it related to the research that you were doing at Stanford University?
A. Well, a in vivo test is one that is performed in life or in the whole body, if you will. It's in an experiment that's conducted in a living animal, such as mice or rats. A in vetro study is one that is performed on individual cells or fractions of cells, and they're usually conducted in test tubes or petri dishes.
Q. Now, you say you left Stanford in about what time period, do you recall?
A. I left Stanford mid 1990.
Q. What did you do after you left Stanford University, the Medical School faculty of Stanford University?
A. I joined a scientific and engineering consulting firm in the San Francisco bay area.
Q. And what kind of scientific consulting -- go ahead and please make liberal use of the water up there.
What kind of scientific consulting did you do after you left Stanford during your work?
A. I consulted in the areas of pharmacology and toxicology, but primarily in the area of toxicology.
Q. You say that you were at this consulting firm for three years. What did you do after your three year stint with the consulting firm?

A. After I left the consulting firm, I formed my own consulting firm, Susan A. Rice and Associates, Inc.
Q. And are you still with Susan A. Rice and Associates, Inc.?
A. Yes, I am.
Q. Not are you still Susan Rice, but you're still with your consulting --
A. I still have the consulting firm, yes.
Q. Very well. And is that a full-time occupation for you, Dr. Rice?
A. Yes, it is.
Q. Tell me the areas in which you and your firm consult and the areas that you've worked in since 1993?
A. Well, as I said, in the areas of pharmacology and toxicology, but it is primarily directed toward the pharmaceutical and medical device industries, where I help my clients to negotiate the regulatory requirements of the FDA, and sometimes other agencies.
Q. Do you ever assist clients in the pharmaceutical industry in performing toxicological studies for purposes of FDA review?
A. Yes. Much of what I do is helping clients to identify the studies need to be performed, analyzing studies if they have been performed previously. And sometimes I would monitor in person the studies. And certainly I look over all studies that are completed under my direction.
I also aid in compiling information, summarizing

information related to studies that are performed and conduct, as needed, literature reviews, and summarize and evaluate that information for the use of my clients, and the presentation to the FDA.

Q. And I think it was in there, but just so I'm clear, do you assist clients, and if you don't perform the study yourself, do you assist the clients in the pharmaceutical industry and other industries in designing a toxicological test that would test for the, or look for toxicity of various chemicals or agents?

A. Yes. But the majority of tests that are required by the regulatory agencies are fairly prescribed, and so there are standard test batteries, if you will. The test batteries depend on the particular indication and -- excuse me -- and the particular part of the agency that you're dealing with.

So I would identify those tests, and then help to find an appropriate contract research organization to perform the work.

I do not perform any of the toxicology tests myself, although, as I said before, I may monitor for my clients.

Q. Dr. Rice, in the course of your work as a consultant in the toxicological industry or art, approximately, how many toxicological -- and I will continue to mispronounce that so I apologize -- how many toxicological reports or studies would you estimate you have reviewed in the course of your career?

A. That's really hard, but it's thousands and thousands.

Q. Dr. Rice, in the course of your career, have you prepared any publications?
A. Yes.
Q. About how many publications have you prepared?
A. I have a total of about 60 publications, which includes about 50 peer-reviewed articles. I have a number of book chapters that I've written for anesthesiology texts and for toxicologists in various areas, and then I've also prepared some technical reports.
Q. Doctor, do you have any credentials or certifications?
A. Yes. I am a Diplomat of the American Board of Toxicology.
Q. So does that mean that you're board certified?
A. Yes, I am board certified in Toxicology.
Q. Dr. Rice, I want you to tell me what the primary focus of your over 30 year career has been as it relates to toxicology?
A. The primary focus of my career has been applied pharmacology and toxicology. And lately it's been more in the applied toxicology arena. And by that I mean that I am not so much interested in the theoretical aspects of toxicology or pharmacology, but I am interested in how the fundamentals of toxicology apply to the real world; and that is, in helping clients to perform appropriate tests and interpreting tests, toxicology tests that have been performed, and then also in evaluating individual exposures to chemicals or interactions with drugs, which becomes a big problem in a lot of drugs that

are submitted for the FDA.

Q. Mr. Russel, could you please pull up DTX1322?

Dr. Rice just so you can kind of get used to the procedure, there is a binder at the witness stand with the exhibits by number with tabs. We will also put up and publish exhibits on the screen, both small and large for you to review, so whatever is easier for you, please feel free to do that.

Well, there will soon be a binder with your exhibits.

A. Thank you.

Q. Yes. All right, let's proceed. Thank you, Mr. Russell. Dr. Rice is DTX-13 -- no, please keep it up, thank you.

Dr. Rice, is DTX-1322 a copy of your curriculum vitae?

A. Yes, it is.

Q. Does 1322 contain a list of some of the publications that you spoke about in your direct?

A. Yes, it does.

Q. Does it indicate your board certification?

A. Yes, it does.

Q. Is 1322 a true and accurate representation of the activities and tasks and positions you've held in the field of toxicology during your career?

A. Yes, it does.

Q. And it is true and accurate, to the best of your knowledge, and current?

A. Yes, it is.

MR. JONES: I move admission of DTX-1322, your Honor.

MR. WIESEN: No objection, your Honor.

THE COURT: Admitted.

(Defendant's Exhibit 1322 received in evidence)

MR. JONES: Thank you, your Honor. And with that, Mylan tenders Dr. Rice as an expert in the field of toxicology.

THE COURT: Any objection?

MR. WIESEN: No objection, your Honor.

THE COURT: All right, Doctor, thank you. Then the Court accepts you as an expert in toxicology.

And I believe that everyone would like to adjourn now.

MR. JONES: That would be fine.

THE COURT: There's one thing I'd like -- Dr. Rice, you can step down. I hope you feel better.

Can I get some idea of who the witnesses are, going into the future after Dr. Rice? I guess I can start with Mylan.

MS. BLOODWORTH: Your Honor, Dr. Rice is Mylan's last witness before we start the --

THE COURT: Before you what?

MS. BLOODWORTH: After Dr. Rice, I believe Sandoz is going to present a couple witnesses next, so maybe Mr. Doyle can talk to that.

THE COURT: Who will they be, Mr. Doyle?

MR. DOYLE: They will be Dr. John Bishop from Momenta,

and then Dr. Carl Scandella. Dr. Laird before Dr. Scandella.

THE COURT: Okay.

MR. DOYLE: Then Dr. Scandella.

THE COURT: All right. And then that would put us at --

MS. BLOODWORTH: And, your Honor, and then Mylan will resume with -- currently we have scheduled for Dr. Mays, although we're still working with Sandoz to see if that's going to be duplicative. So if it's duplicative of Dr. Scandella, we will not call Dr. Mays.

THE COURT: Okay.

MS. BLOODWORTH: To try to streamline things. And then we ever Dr. Ari Green, who is our physician witness, who cannot come in until Monday.

THE COURT: What's his name?

MS. BLOODWORTH: Dr. Green.

THE COURT: Okay.

MS. BLOODWORTH: And we will also be moving in our depositions, et cetera, but that will be the conclusion.

THE COURT: That will be it for live testimony?

MR. DOYLE: Yes, your Honor.

MS. BLOODWORTH: Except for possible rebuttal, your Honor.

THE COURT: All right. And Ms. Holland?

MS. HOLLAND: Yes, your Honor. We will begin our

rebuttal case. We anticipate on Monday with recalling Dr. Grant, followed by Dr. Dubin, and I'm trying to remember the list, but it was Dr. Gokel and Dr. Sampson.

THE COURT: Okay.

MS. HOLLAND: And then we have some maybes, your Honor, but those are the ones that we believe will be called.

THE COURT: You believe at this point you'll be calling.

MS. HOLLAND: Yes.

THE COURT: Okay. So tomorrow we will certainly finish Dr. Rice, and then we'll have Dr. Bishop?

MR. DOYLE: Yes, your Honor.

THE COURT: And possibly --

MR. DOYLE: And I believe we'll conclude Dr. Laird tomorrow as well.

THE COURT: Okay, good. I'll see everybody at 9:30 then.

Is there anything you wanted to raise tonight?

MS. HOLLAND: The only thing, your Honor, that our understanding is that Doctor -- we will begin our rebuttal case after Dr. Green on Monday, the 19th. That's what we're anticipating. I'm not sure what that means about Friday and -- because I'm not sure whether defendants are going to take the full day on Friday or not.

THE COURT: All right.

MR. DOYLE: I think we're likely to take most of Friday, your Honor.

THE COURT: Okay. If you don't, everyone will leave and be very happy. We'll take it from there.

MS. HOLLAND: Thank you.

THE COURT: Okay, see you tomorrow at 9:30 -- including the Reporters.

(Adjourned to September 15th, 2011 at 9:30 a.m.)

INDEX OF EXAMINATION

PLAINTIFF EXHIBITS

DEFENDANT EXHIBITS